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Inhibition of vascular endothelial growth factor (VEGF)-induced endothelial proliferation, arterial relaxation, vascular permeability and angiogenesis by dobesilate.

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Source

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Abstract

Vascular endothelial growth factor (VEGF) is a key factor in angiogenesis and vascular permeability which is associated with many pathological processes. 2,5-hydroxybenzene sulfonate (DHBS; dobesilate) is a small molecule with anti-angiogenic activity that has been described as an inhibitor of fibroblast growth factors (FGF). The aim of the present study was to evaluate the effects of DHBS on VEGF-induced actions. The effects of DHBS were evaluated on VEGF-induced proliferation in human umbilical vein endothelial cells (HUVEC) and rat aorta relaxation, as well as on in vivo VEGF-induced skin vascular permeability and neovascularization in rats. DHBS at 50 and 100 μM concentration significantly inhibited the proliferation of HUVEC induced by VEGF (10 ng/ml), without significantly affecting HUVEC proliferation in the absence of VEGF. Rapid VEGF-induced activation of Akt in HUVEC was also prevented by DHBS (100 μM). Additionally, DHBS (2 μM) specifically inhibited the relaxation of rat aorta induced by VEGF (0.1 to 30 ng/ml), but not endothelium-dependent relaxation to acetylcholine (1 nM to 10 μM). The in vivo enhancement of vascular permeability caused by VEGF injection (50 μl at 10 ng/ml) in rat skin was also inhibited by DHBS co-administration (200 μM) (74.8±3.8% inhibition of dye extravasation). Administration of DHBS (200 mg/kg/day; i.p.) also reduced VEGF-induced angiogenesis in vivo. DHBS inhibits main responses elicited in vitro and in vivo by VEGF. As a dual antagonist of VEGF and FGF activities, DHBS could be of therapeutic interest in the treatment of diseases related to VEGF/FGF overproduction and excessive angiogenesis.

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