Molecular mechanisms mediating the in vitro pro-angiogenic effect of urotensin-II

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Urotensin-II (U-II) is a cyclic peptide synthesized from a large precursor molecule, the prepro-U-II. U-II has been identified as the endogenous ligand of a high-affinity receptor, the urotensin receptor (UT), belonging to the class A of G-protein-coupled receptors. The principal physiological role of U-II in mammals is in the cardiovascular system, where it exerts a potent systemic vasoconstrictor and hypertensive effect and several lines of evidence suggested that U-II might be involved in the pathophysiology of the cardiovascular system and in its structural remodeling as well. In particular, on endothelial cells (EC) of animal origin U-II has been shown to exert a clearcut pro-angiogenic effect. In the present study in vitro models based on human vascular endothelial cells, including saphenous vein, jugular vein, umbilical vein and aorta, have been used to characterize different aspects of the pro-angiogenic profile exhibited by U-II. UT was expressed by all the human EC considered, while the expression of U-II resulted heterogeneous. In the Matrigel assay all the investigated EC exhibited after 18 hours a strong angiogenic response to the peptide. In the presence of specific inhibitors of various steps of the signaling cascade the U-II-induced self organization of the cells in capillary-like structures was PKC dependent and involved the activation of the ERK1/2 and PI3K transduction pathways. For longer times of U-II stimulation the peptide can further enhance the angiogenic process indirectly by inducing in EC a delayed production of pro-angiogenic factors, such as AM, ET-1 and VEGF.