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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.