ALPHA-$_{1D}$ ADRENOCEPTOR STIMULATION INDUCES TROPHIC EFFECTS ON ENDOTHELIAL CELLS: ROLE OF HYPOXIA

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Catecholamines have been shown to be involved in vascular remodeling through the stimulation of α_1-adrenoreceptors (α_1-ARs). Recent studies have revealed that catecholamines are able to increase angiogenesis in pathological conditions, even if the mechanisms and the AR subtypes responsible for the arteriogenic and angiogenic processes still remain unclear. The aim of the present study was to investigate the influence of hypoxia (3%O_2) on the ability of phenylephrine (PHE) to induce a trophic effect in human endothelial cells. PHE was used at concentrations unable to induce any vascular contractile effects. PHE, at picomolar concentrations, significantly promoted pseudocapillary formation from fragments of human mature vessels in vitro. Exposure to hypoxia significantly potentiated this effect, which was inhibited by the selective α_{1D}-AR antagonist BMY 7378 and by the nitric oxide synthase inhibitor L-NAME, suggesting that α_{1D}-adrenoceptors were involved in this effect through activation of the NO pathway. Proliferation and migration of HUVEC were also affected by picomolar PHE concentrations. Again, these effects were significantly potentiated in cells exposed to hypoxia and were inhibited by BMY 3778 and by L-NAME. Conversely, the α_{1A}-AR selective antagonist (S)-(+)-niguldipine hydrochloride and the α_{1B}-AR antagonist cloroethylclonidine dihydrochloride did not modify endothelial cell migration and proliferation in response to PHE. These results demonstrate that the stimulation of α_{1D}-ARs induces a pro-angiogenic phenotype in human endothelial cells which is enhanced in a hypoxic environment and suggest that the role of α_{1D}-ARs may become more prominent in the adaptive responses to hypoxic injury of the vasculature.