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Characteristics of adrenaline-driven receptor-mediated signals in human microvessel-derived endothelial cells

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Abstract:
Adrenaline (0.001–1,000 μM) strongly stimulated adenosine-3',5'cyclic monophosphate (cAMP) generation in cultured human microvascular-derived endothelial cells (HMEC-1). Isoprenaline mimicked the action of adrenaline, whereas noradrenaline appeared to be decisively less potent. Experiments carried out with an array of compounds acting selectively on different types/subtypes of adrenergic receptors revealed that the adrenaline cAMP effect in HMEC-1 cells did not possess either an α_1 or α_2 component. However, the effect may have been mediated through a receptor that did not fit β_1-, β_2-, or β_3-receptor classification. Supporting this assertion, various double and triple β-subtype selective drug combinations maximally inhibited the adrenaline effect by 50–60%, whereas the non-selective antagonist propranolol totally prevented the hormone-evoked cAMP effect. Based on results utilizing the phosphodiesterase (PDE)-isoform nonselective inhibitor 3-isobutyl-1-methylxanthine (IBMX) and the PDE-4-selective inhibitor rolipram, the adrenaline-driven cAMP signal appeared to be regulated by PDE-4. In addition, the present study demonstrated that phenylephrine, a presumed selective α_1-adrenoceptor agonist, was capable of stimulating cAMP generation in HMEC-1 cells in a prazosin-insensitive and propranolol-sensitive manner. This result indicated that in at least this cell model system, phenylephrine may act nonspecifically. Microvessel-derived endothelial cells such as HMEC-1 exhibit functional differences when compared with macrovessel-derived endothelial cells (e.g. HUVEC sensitivity to adrenaline). Accordingly, these cell cultures represent a useful model system to study the biological effects of endogenous catecholamines, including adrenaline, as well as potential therapeutics targeting adrenergic receptors.

Key words:
adrenaline, cyclic AMP, rolipram, PDE-4, phenylephrine, β-adrenoceptor subtype, HMEC-1, human endothelial cell