

β_2 -Adrenoceptor mRNA expression in human lung fibroblasts is highly up-regulated by endothelin-1 (ET-1) and β_2 -adrenoceptors

Lisa J Juergens, Mareille Warnken-Uhlich, Ina Schütz, Margarita Fuhrmann, Racké Racké. Univ. Bonn, Inst. Pharmacology, Germany.

Background: Recent observations indicate that the expression of β_2 -adrenoceptors in human lung fibroblasts is highly regulated via receptor mediated signals, among others it is markedly up-regulated via β_2 -adrenoceptors (e.g. Warnken-Uhlich et al. (2011) Naunyn-Schmiedeberg's Arch Pharmacol 383 (Suppl. 1):46). Since human lung fibroblasts express a functional endothelinergic system (Ahmedat et al. (2010) Naunyn-Schmiedeberg's Arch Pharmacol 381 (Suppl. 1):56; see also Ahmedat et al. this Meeting), the present study aimed to explore possible ET-1-mediated effects on β_2 -adrenoceptor expression in human lung fibroblasts.

Methods: MRC-5 human lung fibroblasts were first cultured for 24 h in presence of 10% FCS. After further 24 h in absence of FCS, cells were exposed to test drugs for 60 - 90 min, followed by β_2 -adrenoceptor mRNA determination by quantitative real time PCR.

Results: The long-acting β_2 -adrenoceptor agonist olodaterol, previously known as BI 1744 CL (1, 10 and 100 nM, 60 min), caused an increase in β_2 -adrenoceptor mRNA expression by $89\pm 21\%$, $122\pm 26\%$ and $110\pm 11\%$ (means \pm s.e.mean), respectively. ET-1 (10 and 100 nM, 60 min) enhanced β_2 -adrenoceptor mRNA expression by $81\pm 19\%$ and $64\pm 11\%$, respectively. Combined presence of olodaterol (100 nM) and ET-1 (10 or 100 nM) resulted in an increase in β_2 -adrenoceptor mRNA expression by $286\pm 52\%$ and $213\pm 42\%$, respectively. The role of ET-A and/or ET-B receptors for the up-regulation of β_2 -adrenoceptor is currently under investigation by use of subtype selective antagonists BQ123 and BQ788. Forskolin (10 μ M, 60 min) and the EP₂-selective agonist butaprost (100 nM, 60 min) induced also an increase in β_2 -adrenoceptor mRNA expression by $90\pm 13\%$ and $95\pm 15\%$, respectively. However, combined presence of olodaterol with either forskolin or butaprost did not result in any additive effects, in contrast to the additive interaction between olodaterol and ET-1.

Conclusions: ET-1 receptors and β_2 -adrenoceptors can mediate additive stimulatory effects on the expression of β_2 -adrenoceptors mRNA in human lung fibroblasts, indicating that G_s and G_q coupled receptors may synergistically contribute to the maintenance of β_2 -adrenoceptor expression in these cells.

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