

P014 Contractile responses through G_s -coupled receptors are reduced by phosphodiesterase3 activity in human isolated myocardium

¹Christ, T., ²Molenaar, P., ³Galindo-Tovar, A., ¹Ravens, U. & ⁴Kaumann, A.J.

¹Pharmacology Department TU Dresden, Germany;

²Medicine Department, University of Queensland, Australia;

³H.U.V.A., Murcia, Spain; ⁴Physiology Department, University of Cambridge, UK.

The cAMP hydrolysing phosphodiesterases PDE3 and PDE4 coexist in mammalian cardiomyocytes but their role in modulating contractile force increases through G_s -coupled receptors in human myocardium is unknown. We investigated the influence of the PDE3 inhibitor cilostamide (100-300 nM) and PDE4 inhibitor rolipram (1 μ M) on the positive inotropic responses to noradrenaline (β_2 -selective antagonist ICI118551, 50 μ M present) and adrenaline (β_1 -selective antagonist CGP20712, 300 μ M present), mediated through β_1 - and β_2 -adrenoceptors respectively. In ventricular trabeculae from 5 patients with terminal heart failure, cilostamide increased the $-\log EC_{50}$ M of noradrenaline from 5.66 ± 0.20 to 5.96 ± 0.15 ($P < 0.05$) and for adrenaline from 5.09 ± 0.47 to 6.32 ± 0.53 ($P = 0.08$). In atrial trabeculae from 8 patients without heart failure, cilostamide increased the $-\log EC_{50}$ M of adrenaline and noradrenaline from 7.54 ± 0.13 and 7.08 ± 0.19 to 8.27 ± 0.12 ($P < 0.005$) and 7.30 ± 0.30 ($P = 0.05$) respectively. 5-hydroxytryptamine (5-HT, 1 μ M) increased contractility of atrial trabeculae from 6 non-failing hearts; the responses faded by $93 \pm 4\%$ 60 min after administration. Cilostamide reduced the fade to $50.5 \pm 8\%$ ($P < 0.003$). Rolipram failed to affect the responses to adrenaline, noradrenaline and 5-HT. PDE3, but not PDE4, protects the human heart against overstimulation through β_1 -adrenoceptors, β_2 -adrenoceptors and 5-HT₄ receptors.