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First In Human Study of a Novel Biased Apelin Receptor Ligand, MM54, A G-alpha(i) Agonist/ Beta-arrestin Antagonist

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Introduction: The peptide apelin acts via G proteins to cause beneficial vasodilation and potent positive inotropy to ameliorate pulmonary arterial hypertension in humans and animal models. Apelin is internalised via β-arrestin. In contrast, with loss of endogenous apelin, its receptor acts as a mechanosensor, stimulating β-arrestin to induce detrimental cardiac hypertrophy. Our aim was to characterise the action of our apelin ligand, MM54 that in cell based assays blocks β-arrestin but activates the Gαi protein pathway, in this first in human study.

Method: Competition binding in human heart (n=3) used [I^{125}] [Pyr^{1}]apelin-13 (0.1nmol/L). β-arrestin recruitment, receptor internalization and forskolin-induced cAMP inhibition were measured in CHO-K1 cells expressing human apelin receptor. Forearm blood flow was measured in 9 volunteers using venous occlusion plethysmography at baseline and at 4 incremental doses (1, 10, 30, 100 nmol/min) of MM54, each for eight minutes. The Aellig hand vein technique was used to measure the effect of 3 incremental doses (3, 30, 300 nmol/min) of MM54 for 15 min on veins pre-constricted with noradrenaline in 6 individuals compared with 8 controls. Data are mean+SEM, n≥3.

Results: MM54 had an affinity of pKi = 6.50±0.03. In β-arrestin (pK_B 6.93±0.15) and receptor internalization assays (pK_B 5.89±0.06) MM54 was an antagonist, but activated the G protein pathway (pD_2±SEM 5.86+0.23). At the highest concentration (100 nmol/min), MM54 caused a significant absolute increase in forearm blood flow compared to control arm, representing a 76 % change from baseline (P<0.01, ANOVA with repeated measures with Dunnett's post hoc analysis on untransformed data). In the hand vein, MM54 caused a significant concentration dependent dilatation in veins over the concentration range tested, with the highest dose causing 57% reversal (P<0.01).

Conclusion: At the cellular level, the results suggest MM54 induced a different conformation in the receptor compared with the native peptide apelin, resulting in a biased profile of activating the G protein pathway but blocking β-arrestin. In agreement in clinical studies, in both the arterial and venous circulation, MM54 induced vasodilatation that is thought to be mediated by the G protein pathway.

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