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Development of novel selective beta 1-adrenoceptor antagonists for concomitant cardiovascular and respiratory disease

J. G. Baker, S. M. Gardiner, J. Woolard, C. Fromont, G. P. jadhav, S. N. Mistry, K. s. Thompson, B. Kellam, S. J. Hill, P. M. Fischer. university of nottingham, nottingham, UNITED KINGDOM.

Introduction. β-blockers reduce mortality in people with heart disease. Clinical β-blockers have poor cardioselectivity (β1-adrenoceptor (AR) affinity) over the lung β2-AR. Unwanted β2-blockade risks causing life-threatening bronchospasm and reducing the effectiveness of β2-agonist emergency rescue therapy. Consequently, people with heart disease and asthma are unable to take current life-prolonging β-blockers. In order to overcome this limitation, we have synthesized highly β1-selective compounds.

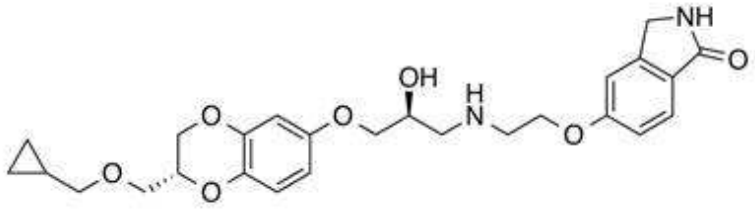
Method. From over 1000 novel β-blockers, NDD-825 was chosen for detailed evaluation. Studies involved ^{3}H-CGP12177 whole cell binding, ^{3}H-cAMP accumulation, ERK1/2 MAP Kinase activity assays (CHO-β1 and CHO-β2 cells [1]) and monitoring heart rate (HR) and hind quarters conductance (HQC) in conscious Sprague-Dawley rats [2].

Results. ^{3}H-CGP12177 binding yielded a log K_D of -8.28±0.05 (n=20) for the human β1-AR, and -5.27±0.03 (n=16) for the human β2-AR (β1-selectivity of 1023-fold). NDD-825 did not stimulate any ^{3}H-cAMP accumulation response (β1 or β2-AR, n=8), although NDD-825 caused rightward parallel shifts of cimaterol dose response curves (yielding log K_D values of β1 -8.99±0.05 (n=9; Schild plot 1.04±0.02, n=3) and β2 -5.75±0.06 (n=4); β1-selectivity 1738-fold). No NDD-825 responses were observed for CRE-gene transcription (n=5), or direct measures of ERK1/2 phosphorylation (n=4). In a panel of 80 GPCRs and ion channels, only binding to the 5-HT2A receptor was detected (5.8μM, β1-selectivity of 1115-fold). In rats, NDD-825 (iv bolus 2mg/kg, infusion 1mg/kg/h) suppressed β1-mediated HR (basal and isoprenaline-induced HR) but had no effect on β2-mediated HQC responses (n=4 rats), with HR still suppressed 24h post NDD-825 infusion. Given orally, 3 and 10mg/kg NDD-825 reduced basal and isoprenaline-induced HR with no effect on HQC (n=3 rats). NDD-825 had a long pharmacokinetic clearance with a single oral dose of 20mg/kg never reaching plasma concentrations sufficient to block the β2-AR, despite remaining above that required for β1-blockade for 24hr. NDD-825 (10μM) had no cytotoxic effects (HepG2 cell viability assays), no hERG channel affinity and no genotoxicity effects (AMES test). ADME properties were good and NDD-825 was well tolerated at the highest dose tested (300mg/kg daily) in a 7-day repeat-dose oral rat toxicology study, without any macro- or microscopic changes at autopsy.

Conclusion. NDD-825 is an orally bioavailable highly β1-selective β-blocker, with no intrinsic efficacy, no apparent off-target interactions, good disposition properties and no adverse toxicological effects. NDD-825 offers a truly cardioselective β-blocker that may benefit people with both heart and respiratory disease.

References.

1. Baker JG et al., (2011) FASEB J 25:4486-4497.
2. Baker JG et al., (2013) PLoS ONE 8(11): e77582. doi:10.1371/journal.pone.0077582



NDD-825