In vitro and in vivo analysis of a novel highly selective β1-adrenoceptor partial agonist.

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β-adrenoceptor antagonists (β-blockers) are widely used and save lives in people with heart disease due to blockade of β1-adrenoceptors in the heart. Unfortunately, current β-blockers have poor β1 vs β2-adrenoceptor selectivity and are therefore contraindicated in people with asthma due to their bronchoconstrictor effects via the β2-adrenoceptors in the lungs. This means that people with both asthma and heart disease are unable to take these life prolonging drugs. We have previously investigated current β-blockers and found them to have poor selectivity in both cellular assays and in whole animals (Baker et al., 2011).

We therefore initiated a programme to develop highly selective β1-antagonists. Here we report a novel and highly selective partial agonist for the □1-adrenoceptor: SM64 1-{2-[(3-{4-[2-(cyclopropylmethoxy)ethoxy]phenoxy}-2-hydroxypropyl)amino]ethyl}-3-(4-hydroxyphenyl)urea.

The pharmacological properties of SM64 were investigated using ^{3}H-cAMP accumulation in cells stablyl expressing the human β1 and β2-adrenoceptors and in conscious, atropine-treated freely moving, adult male Sprague-Dawley rats, instrumented for measurement of heart rate (β1) and hindquarters conductance (β2) as previously described (Baker et al., 2011).

At the human β1-adrenoceptor, SM64 stimulated an increase in ^{3}H-cAMP accumulation (log EC_{50} = -8.05 ± 0.04, 51.7 ± 1.7% maximum isoprenaline, n=5). It behaved as a typical partial agonist, inhibiting cimaterol agonist responses to give a log K_D of -7.76 ± 0.06 n=15 (by the partial agonist method of Stephenson, 1956). Even at maximal concentrations (10μM, stimulation 9.3 ± 0.09% isoprenaline maximum, n=5) it caused minimal shift of the cimaterol concentration response curve at the human β2-adrenoceptor giving a log K_D of -5.01 ± 0.07 (n=5). SM64 is therefore 457 times β1 over β2 selective.

In conscious rats, SM64 (2mg/kg bolus, 1mg/kg/h infusion) caused an increase in basal heart rate (from 424 ± 9 bpm to 465 ± 3bpm = 44% of the response to 120ng/kg/min isoprenaline, n=4 animals) in keeping with its partial agonist actions observed in the cell studies. Furthermore SM64 significantly inhibited the β1-mediated heart rate responses to isoprenaline (at 12, 40 and 120ng/kg/min) whilst having no effect on the β2-mediated hindquarters response (n=4 rats), consistent with its β1-selectivity.

In conclusion, SM64 is a high affinity β1-adrenoceptor partial agonist as demonstrated in cell studies and in conscious rats. A molecule of this selectivity or greater, devoid of partial agonist effects, could prove a very useful therapy for people with heart disease and asthma.

Baker et al., 2011 FASEB J 25: 4486-4497

Stephenson 1956 Br J Pharmacol 11: 5109-5116