

In vitro and in vivo analysis of a novel highly selective β_1 -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 β_1 -adrenoceptors in the heart. Unfortunately, current β -blockers have poor β_1 vs β_2 -adrenoceptor selectivity and are therefore contraindicated in people with asthma due to their bronchoconstrictor effects via the β_2 -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 β_1 -antagonists. Here we report a novel and highly selective partial agonist for the β_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 ^3H -cAMP accumulation in cells stably expressing the human β_1 and β_2 -adrenoceptors and in conscious, atropine-treated freely moving, adult male Sprague-Dawley rats, instrumented for measurement of heart rate (β_1) and hindquarters conductance (β_2) as previously described (Baker et al., 2011).

At the human β_1 -adrenoceptor, SM64 stimulated an increase in ^3H -cAMP accumulation ($\log EC_{50} = -8.05 \pm 0.04$, $51.7 \pm 1.7\%$ 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 ($10\mu\text{M}$, stimulation $9.3 \pm 0.09\%$ isoprenaline maximum, $n=5$) it caused minimal shift of the cimaterol concentration response curve at the human β_2 -adrenoceptor giving a $\log K_D$ of -5.01 ± 0.07 ($n=5$). SM64 is therefore 457 times β_1 over β_2 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 ± 3 bpm = 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 β_1 -mediated heart rate responses to isoprenaline (at 12, 40 and 120ng/kg/min) whilst having no effect on the β_2 -mediated hindquarters response ($n=4$ rats), consistent with its β_1 -selectivity.

In conclusion, SM64 is a high affinity β_1 -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