### Adrenoceptors, β

**Overview:** β-Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, see Bylund et al., 1994) are GPCR activated by the endogenous agonists adrenaline and noradrenaline. Isoprenaline is a synthetic agonist selective for β-adenoreceptors relative to α1- and α2-adenoreceptors, while propranolol (pK<sub>A</sub> 8.2–9.2) and cyanopindolol (pK<sub>A</sub> 10.0–11.0) are relatively selective antagonists. β<sub>1</sub>-Adrenoceptors are relatively resistant to blockade by propranolol (pK<sub>A</sub> 5.8–7.0), but can be blocked by high concentrations of bupranolol (pK<sub>A</sub> 8.65, Sato et al., 2008). Numerous polymorphisms exist for the β<sub>1</sub>- and β<sub>2</sub>-adrenoceptors and some of these are associated with alterations in signalling in response to agonists. These polymorphisms are likely to be associated with disease susceptibility and altered responses to drugs. The X-ray crystal structures have recently been described of the agonist bound (Warne et al., 2011) and antagonist bound forms of the β<sub>1</sub>- (Warne et al., 2008), agonist-bound (Cherezov et al., 2007) and antagonist-bound forms of the β<sub>2</sub>-adrenoceptor (Rosenbaum et al., 2011; Rasmussen et al., 2011a), as well as agonist-bound, G<sub>i</sub> protein-coupled β<sub>2</sub>-adrenoceptor (Rasmussen et al., 2011b).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>β&lt;sub&gt;1&lt;/sub&gt;</th>
<th>β&lt;sub&gt;2&lt;/sub&gt;</th>
<th>atypical β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>–</td>
<td>–</td>
<td>atypical β</td>
</tr>
<tr>
<td>Ensembl ID</td>
<td>ENSG00000043591</td>
<td>ENSG00000169252</td>
<td>ENSG00000188778</td>
</tr>
<tr>
<td>Principal transduction</td>
<td>G&lt;sub&gt;i&lt;/sub&gt;</td>
<td>G&lt;sub&gt;i&lt;/sub&gt;</td>
<td>G&lt;sub&gt;i&lt;/sub&gt;</td>
</tr>
<tr>
<td>Rank order of potency</td>
<td>Noradrenaline&lt;nobr&gt;-&lt;/nobr&gt;adrenaline</td>
<td>Adrenaline&lt;nobr&gt;-&lt;/nobr&gt; noradrenaline</td>
<td>Noradrenaline&lt;nobr&gt;-&lt;/nobr&gt;adrenaline</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>Noradrenaline, xamoterol, RO363, denopamine</td>
<td>Procatelol, salbutamol, zinterol, salmeterol, fomoterol, terbutaline, fenoterol (Baker, 2010)</td>
<td>BRL37344, CL316243, CGP12177A, carazolol, L742791, L755507, SB251023</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>CGP20712A (8.5–9.3), betaxolol (8.5), atenolol (7.6)</td>
<td>ICI185551 (8.3–9.2)</td>
<td>SR59230A (8.8), L748337 (8.4)</td>
</tr>
<tr>
<td>Probes</td>
<td>[³²P]-ICYP (20–50 pM)+70 nM</td>
<td>[³²P]-ICYP (20–50 pM)+100 nM</td>
<td>[³²P]-ICYP (0.5 nM)</td>
</tr>
</tbody>
</table>

Noradrenaline, xamoterol and RO363 are agonists that show selectivity for β<sub>1</sub>-relative to β<sub>2</sub>-adrenoceptors. Pharmacological differences exist between human and mouse β<sub>1</sub>-adrenoceptors, and the ‘rodent selective’ agonists BRL37344 and CL316243 have low efficacy at the human β<sub>1</sub>-adrenoreceptor whereas CGP12177A and L755507 activate human β<sub>2</sub>-adrenoceptors (Sato et al., 2008). All β<sub>2</sub>-adrenoceptors couple to G<sub>i</sub>, (activating adenylyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate other G proteins such as G<sub>q</sub> and many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at β<sub>1</sub>- and β<sub>2</sub>-adrenoceptors are agonists at β<sub>1</sub>-adrenoceptors (CL316243, CGP12177A and carazolol). Many ‘agonists’ appear to be able to selectively activate mitogen-activated protein kinase pathways (Baker et al., 2003; Galianro and Bouvier, 2006; Galianro et al., 2008; Sato et al., 2007; Sato et al., 2008; Evans et al., 2010) and display ligand-directed signalling bias. Bupranolol appears to act as a neutral antagonist in most systems so far examined. SR59230A has reasonably high affinity at β<sub>2</sub>-adrenoceptors (Manara et al., 1996), but does not discriminate well between the three β-adrenoceptor subtypes (Candorel et al., 1999) and has been reported to have lower affinity for the β<sub>2</sub>-adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

The β<sub>β</sub>-adrenoceptor has introns, but splice variants have only been described for the mouse (Evans et al., 2011), where the isoforms display different signalling characteristics (Hutchinson et al., 2002). There are 3 β-adrenoceptors in turkey (termed the β<sub>β</sub>, β<sub>β</sub>C and β<sub>β</sub>C) that have a pharmacology that differs from the human β-adrenoceptors (Baker, 2011). The ‘putative β<sub>β</sub>-adrenoceptor’ is not a novel receptor but is likely to represent an alternative site of interaction of CGP12177A and other nonconventional partial agonists at β<sub>2</sub>-adrenoceptors, since ‘putative β<sub>β</sub>-adrenoceptor’-mediated agonist effects of CGP12177A are absent in mice lacking β<sub>2</sub>-adrenoceptors (Konk et al., 2000; Kaumann et al., 2001).

Radioligand binding with [³²P]-ICYP can be used to define β<sub>1</sub>- or β<sub>2</sub>-adrenoceptors when conducted in the presence of a ‘saturating’ concentration of either a β<sub>1</sub>- or β<sub>2</sub>-adrenoceptor-selective antagonist. [³²P]-CGP12177 or [³²P]-dihydroalprenolol can be used in place of [³²P]-ICYP. Binding of a fluorescent analogue of CGP12177 to β<sub>1</sub>-adrenoceptors in living cells has been described (Baker et al., 2003a). [³²P]-ICYP at higher (nM) concentrations can be used to label β<sub>1</sub>-adrenoceptors in systems where there are few if any other β-adrenoceptor subtypes.
Abbreviations: BRL37344, sodium 4-[[2-hydroxy-3-chlorophenyl]ethylamino]propyl]phenoxyacetate; CGP2177A, (-)-(3-(tert-butylamino)-2-hydroxypropoxy)-benzimidazol-2-one; CGP20712A, 2-hydroxy-5-[[2-hydroxy-3-(4-1-methyl-4-trifluoromethyl-2-imidazolyl)phenoxo]propyl]amino]ethoxybenzamide; CL316243, (S)-3,4-dimethoxyphenethylamino]-3-(3,4-dihydroxyphenoxy]-2-propanoloxalate; ICYP, iodocyanopindolol; L742791, (S)-N-[[4-[[3-[4-hydroxyphenoxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide; L748337, N-[[3-[4-(2-hydroxy-3-[[2-[4-[(phenylsulfonyl)amino]phenyl]ethyl]amino]propoxy]phenyl][methyl]acetamide; RO363, (S)-1-3,4-dimethoxyphenethylamino]-3-(3,4-dihydroxyphenoxy]-2-propanoloxalate; SB251033, (S)-1-[2-[4-(4- hydroxyphenoxy)-propylamino]cyclopentylmethyl]phenoxy)methyl]phenolphosphonic acid lithium salt; SR59230A, 3-(2-ethylphenoxy)-1[[1s]-1,2,3,4-tetrahydronaphth-1-ylamino]-2-s-propanol oxalate

For more information on related products, please visit www.aladdin-e.com

Further Reading


References


(Source: BRITISH JOURNAL OF PHARMACOLOGY)