Adrenoceptors, β

Overview: β-Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are 7TM receptors, activated by the endogenous agonists adrenaline and noradrenaline. Isoprenaline is a synthetic agonist selective for β-adrenoceptors relative to α_1- and α_2-adrenoceptors, while propranolol (pK_i 8.2–9.2) and cyanopindolol (pK_i 10.0–11.0) are relatively selective antagonists. β_3-Adrenoceptors are relatively resistant to blockade by propranolol (pK_i 5.8–7.0), but can be blocked with high concentrations of cyanopindolol (pK_i 9.0). Numerous polymorphisms exist for the β_1- and β_2-adrenoceptors and some of these are associated with alterations in signalling in response to agonists. These polymorphisms are likely to be associated with altered responses to drugs. The X-ray crystal structures of the β_1- (Warne *et al.*, 2008) and β_2-adrenoceptors (Cherezov *et al.*, 2007) have been solved.

Nomenclature	β_1	β_2	β_3
Other names	–	–	atypical β
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000147477
Principal transduction	G_s	G_s	G_s
Rank order of potency	Noradenaline > adrenaline	Adrenaline > noradenaline	Noradenaline = adrenaline
Selective agonists	Noradrenaline, xamoterol, RO363, denopamine	Procaterol, zinterol, salmeterol, formoterol, terbutaline, fenoterol	BRL37344, CL316243, CGP12177A, carazolol, L742791, SB251023
Selective antagonists	CGP20712A (8.5–9.3), betaxolol (8.5), atenolol (7.6)	ICI118551 (8.3–9.2)	SR59230A (8.8), L748328 (8.5)
Probes	[^{125}I]-ICYP (20–50 pM) + 70 nM ICI118551	[^{125}I]-ICYP (20–50 pM) + 100 nM CGP20712A	[^{125}I]-ICYP (0.5 nM)

Noradrenaline, xamoterol and RO363 show selectivity for β_1- relative to β_2-adrenoceptors. All β-adrenoceptors couple to G_s (activating adenylyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate other G proteins such as G_i and many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at β_1- and β_2-adrenoceptors are agonists at β_3-adrenoceptors (CL316243, CGP12177A and carazolol). Many 'antagonists' appear to be able to selectively activate mitogen-activated protein kinase pathways (Baker *et al.*, 2003a; Galandrin and Bouvier, 2006; Sato *et al.*, 2007; Galandrin *et al.*, 2008; Sato *et al.*, 2008). SR59230A has reasonably high affinity at β_3-adrenoceptors (Manara *et al.*, 1996), but does not discriminate well between the three β-adrenoceptor subtypes (Candelore *et al.*, 1999) and has been reported to have lower affinity for the β_3-adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

Pharmacological differences exist between human and mouse β_3-adrenoceptors, and the 'rodent selective' agonists BRL37344 and CL316243 have low efficacy at the human β_3-adrenoceptor. The β_3-adrenoceptor has introns, but splice variants have only been described for the mouse (Evans *et al.*, 1999). The β-adrenoceptor cloned from turkey (termed the β4c, t428 SwissProt P43141) has a pharmacology that is intermediate between β_2- and β_3-adrenoceptors (Chen *et al.*, 1994). The 'putative β_4-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_1-adrenoceptors, as 'putative β_4-adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking β_1-adrenoceptors (Konkar *et al.*, 2000; Kaumann *et al.*, 2001).

Radioligand binding to define β_1- and β_2-adrenoceptors can be conducted in the presence of a 'saturating' concentration of a β_1- or β_2-adrenoceptor-selective antagonist. [^{3}H]-CGP12177 or [^{3}H]-dihydroalprenolol can be used in place of [^{125}I]-ICYP. Binding of a fluorescent analogue of CGP12177 to β_2-adrenoceptors in living cells has been described (Baker *et al.*, 2003b). [^{125}I]-ICYP at higher (nM) concentrations can be used to label β_3-adrenoceptors in systems where there are few if any other β-adrenoceptor subtypes.

Abbreviations: BRL37344, sodium 4-(2-[2-hydroxy-3-chlorophenyl}ethylamino]propyl)phenoxyacetate; **CGP12177A**, (-)-4-(3-tert-butylamino-2-hydroxypropoxy)-benzimidazol-2-one; **CGP20712A**, 2-hydroxy-5-(2-[{2-hydroxy-3-(4-[1-methyl-4-trifluoromethyl-2-imidazolyl]phenoxy) propyl}amino]ethoxy)benzamide; **CL316243**, disodium (*R*,*R*)-5-(2-[{2-(3-chlorophenyl)-2-hydroxyethyl}-amino]propyl)-1,3-benzodioxole-2,2,dicarboxylate; **ICYP**, iodocyanopindolol; **L742791**, (*S*)-*N*-(4-[2-{(3-[4-hydroxyphenoxy]-2-hydroxypropyl)amino}ethyl]phenyl)-4-iodobenzenesulfonamide; **L748328**, (*S*)-*N*-(4-[2-{(3-[3-{aminosulfonyl}phenoxy]-2-hydroxypropyl)-amino}ethyl]phenyl)benzenesulfonamide; **RO363**, (-)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihdroxyphenoxy)-2-propanol)oxalate; **SB251023**, (4-[1-{2-(*S*)-hydroxy-3-(4-hydroxyphenoxy)-propylamino}cyclopentylmethyl]phenoxymethyl)phenylphosphonic acid lithium salt; **SR59230A**, 3-(2-ethylphenoxy)-1([1s]-1,2,3,4-tetrahydronaphth-1-ylamino)-2*S*-propanol oxalate

Further Reading

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