

# Adrenoceptors, $\beta$

**Overview:**  $\beta$ -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  $\beta$ -adrenoceptors relative to  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors, while propranolol ( $pK_i$  8.2–9.2) and cyanopindolol ( $pK_i$  10.0–11.0) are relatively selective antagonists.  $\beta_3$ -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  $\beta_1$ - and  $\beta_2$ -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.

Nomenclature	$\beta_1$	$\beta_2$	$\beta_3$
Other names	—	—	atypical $\beta$
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000147477
Principal transduction	$G_s$	$G_s$	$G_s$
Rank order of potency	Noradrenaline > adrenaline	Adrenaline > noradrenaline	Noradrenaline = 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	[ <sup>125</sup> I]-ICYP (20–50 pM) + 70 nM ICI118551	[ <sup>125</sup> I]-ICYP (20–50 pM) + 100 nM CGP20712A	[ <sup>125</sup> I]-ICYP (0.5 nM)

Noradrenaline, xamoterol and RO363 show selectivity for  $\beta_1$ - relative to  $\beta_2$ -adrenoceptors. All  $\beta$ -adrenoceptors couple to  $G_s$  (activating adenylyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at  $\beta_1$ - and  $\beta_2$ -adrenoceptors are agonists at  $\beta_3$ -adrenoceptors (CL316243, CGP12177A and carazolol). Many 'antagonists' appear to be able to activate selectively mitogen-activate protein kinase pathways (Baker *et al.*, 2003a; Galandrin and Bouvier, 2006; Sato *et al.*, 2007). SR59230A has reasonably high affinity at  $\beta_3$ -adrenoceptors (Manara *et al.*, 1996), but does not discriminate well between the three  $\beta$ -adrenoceptor subtypes (Candelore *et al.*, 1999) and has been reported to have lower affinity for the  $\beta_3$ -adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

Pharmacological differences exist between human and mouse  $\beta_3$ -adrenoceptors, and the 'rodent selective' agonists BRL37344 and CL316243 have low efficacy at the human  $\beta_3$ -adrenoceptor. The  $\beta_3$ -adrenoceptor has introns, but splice variants have only been described for the mouse (Evans *et al.*, 1999). The  $\beta$ -adrenoceptor cloned from turkey (termed the  $\beta_{4c}$ , t428 SwissProt P43141) has a pharmacology that is intermediate between  $\beta_2$ - and  $\beta_3$ -adrenoceptors (Chen *et al.*, 1994). The 'putative  $\beta_4$ -adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP12177A and other nonconventional partial agonists at  $\beta_1$ -adrenoceptors, since 'putative  $\beta_4$ -adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking  $\beta_1$ -adrenoceptors (Konkar *et al.*, 2000; Kaumann *et al.*, 2001).

Radioligand binding to define  $\beta_1$ - and  $\beta_2$ -adrenoceptors can be conducted in the presence of a 'saturating' concentration of the  $\beta_1$ - or  $\beta_2$ -adrenoceptor-selective antagonist. [<sup>3</sup>H]-CGP12177 or [<sup>3</sup>H]-dihydroalprenolol can be used in place of [<sup>125</sup>I]-ICYP. Binding of a fluorescent analogue of CGP12177 to  $\beta_2$ -adrenoceptors in living cells has been described (Baker *et al.*, 2003b).

**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-iodobenzene-sulfonamide; L748328, (S)-N-(4-[2-[(3-[3-aminosulfonyl]phenoxy]-2-hydroxypropyl)-amino]ethyl]phenyl)benzenesulfonamide; RO363, (-)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propanol)oxalate; SB251023, (4-[1-[2-(S)-hydroxy-3-(4-hydroxyphenoxy)-propyl-amino]cyclopentylmethyl]phenoxy)methyl)phenylphosphonic acid lithium salt; SR59230A, 3-(2-ethylphenoxy)-1-[(1s)-1,2,3,4-tetrahydronaphth-1-ylamino]-2S-propanol oxalate

## Further Reading

Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP *et al.* (1994). International Union of Pharmacology IV. Nomenclature of adrenoceptors. *Pharmacol Rev* 46: 121–136.  
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## References

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## Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* 153 (Suppl. 2): S1–S209.