

## Adrenoceptors in GtoPdb v.2026.1

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### Abstract

**The nomenclature of the Adrenoceptors has been agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [121, 327].**

#### Adrenoceptors, $\alpha_1$

There are three  $\alpha_1$ -adrenoceptor subtypes  $\alpha_{1A}$ ,  $\alpha_{1B}$  and  $\alpha_{1D}$  are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Signalling is predominantly via  $G_{q/11}$  but  $\alpha_1$ -adrenoceptors can also couple to  $G_{i/o}$ ,  $G_s$  and  $G_{12/13}$  [505]. Adrenoceptors are primarily located in blood vessels and in the brain, with the  $\alpha_{1A}$  subtype also present in the urogenital tract.

*Clinical uses:*  $\alpha_1$ -Adrenoceptor antagonists are used to treat hypertension (doxazosin, terazosin [436]), hypertension in pregnancy (labetalol), benign prostatic hyperplasia (alfuzosin, doxazosin, terazosin, tamsulosin and silodosin [317]), PTSD (doxazosin, prazosin) and phaeo-chromocytoma (phenoxybenzamine, phentolamine).

$\alpha_{1A}$ -Adrenoceptor agonists are used short-term as nasal decongestants (xylometazoline and oxymetazoline), although they also activate imidazoline and  $\alpha_{2A}$ -receptors. Adrenaline and noradrenaline can be given by infusion to treat hypotension in shock.

*Antagonists:* High affinity, non-selective  $\alpha_1$ -adrenoceptor antagonists include (+)-cyclazosin, doxazosin, prazosin and terazosin. Fluorescent derivatives of prazosin (BODIPY FL-prazosin) are used to examine cellular localisation of  $\alpha_1$ -adrenoceptors. [<sup>3</sup>H]prazosin and [<sup>125</sup>I]HEAT (BE2254) are  $\alpha_1$ -selective antagonist radioligands.  $\alpha_{1A}$ -Subtype selective antagonists include SNAP5089, silodosin, RS-100329 and S(+)-niguldipine (although this also has high affinity for L-type  $Ca^{2+}$  channels). Several anti-depressants and anti-psychotic drugs also have high  $\alpha_{1A}$ -adrenoceptor antagonist affinity that may contribute to their CNS actions but likely also contribute to side effects such as orthostatic hypotension [312]. BMY-7378 has  $\alpha_{1D}$ -subtype selectivity.

*Agonists:* High efficacy non-selective  $\alpha_1$ -adrenoceptor agonists include phenylephrine, methoxamine, etilefrine, naphazoline and cirazoline (relative to  $\alpha_2$ - and  $\beta$ -adrenoceptors). A61603 is selective for the  $\alpha_{1A}$ -subtype.

*Species differences:* Few species differences have been reported for  $\alpha_1$ -adrenoceptor ligands.

#### Adrenoceptors, $\alpha_2$

There are three  $\alpha_2$ -adrenoceptor subtypes  $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_{2C}$  that are activated by the endogenous agonists (-)-adrenaline and with lower potency by (-)-noradrenaline.  $\alpha_2$ -Adrenoceptor signalling is

predominantly *via*  $G_{i/o}$  but they can also couple to  $G_s$ .  $\alpha_2$ -Adrenoceptors cause inhibition of voltage dependent  $Ca^{2+}$  channels and augment inwardly rectifying  $K^+$  channels [213, 505]. All  $\alpha_2$ -adrenoceptor subtypes may be located pre- or post-junctionally and are primarily located in brain and kidney with  $\alpha_{2A}$ - and  $\alpha_{2C}$ - subtypes present in blood vessels and  $\alpha_{2A}$ - in spleen and pancreas.

*Clinical uses:*  $\alpha_2$ -Adrenoceptor antagonists are not used clinically.  $\alpha_2$ -Adrenoceptor agonists are used to treat hypertension (clonidine, moxonidine, acting *via* central baroreflex control), to induce analgesia, sedation and anxiolysis (dexmedetomidine), for ADHD (guanfacine), in glaucoma and rosacea (brimonidine (UK14304)) and muscle spasm (tizanidine), as short-term nasal decongestants (xylometazoline and oxymetazoline that also activate imidazoline [101] and  $\alpha_{1A}$  receptors), and increasingly to treat opioid withdrawal.

*Antagonists:* High affinity, non-subtype selective  $\alpha_2$ -adrenoceptor antagonists include rauwolscine, yohimbine, RX821002, atipamezole and RS79948 [65]. [ $^3H$ ]rauwolscine and [ $^3H$ ]RX821002 are  $\alpha_2$ -selective antagonist radioligands. BRL 44408 has some  $\alpha_{2A}$ -selectivity and MK-912 and JP1302 some  $\alpha_{2C}$ -selectivity. idazoxan, an early  $\alpha_2$ -adrenoceptor antagonist, also has significant binding to imidazoline receptors [101] (and 5-HT receptors).

*Agonists:* brimonidine (UK14304) is a high efficacy non-subtype selective  $\alpha_2$ -adrenoceptor agonist (relative to  $\alpha_1$ - and  $\beta$ -adrenoceptors). Other agonists include talipexole, apraclonidine (para-aminoclonidine), clonidine, guanfacine, medetomidine and dexmedetomidine. [ $^3H$ ]brimonidine (UK14304) is an  $\alpha_2$ -selective agonist radioligand. oxymetazoline has significant  $\alpha_2$ -adrenoceptor agonism, but it is also an  $\alpha_{1A}$  and imidazoline receptor agonist [101].

*Species differences:* There are species variations in the pharmacology of the  $\alpha_{2A}$ -adrenoceptor with regard to antagonists although agonist pharmacology is very similar.

## Adrenoceptors, $\beta$

There are three  $\beta$ -adrenoceptor subtypes  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  that are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Signalling is predominantly *via*  $G_s$ , although there are reports of  $G_i$ -coupling and ERK1/2 phosphorylation, and the  $\beta_2$ -adrenoceptor also activates  $\beta$ -arrestin-mediated signalling [505].  $\beta_1$ -Adrenoceptors are primarily present in heart, blood vessels, kidney and brain;  $\beta_2$ -adrenoceptors in lungs, blood vessels, skeletal muscle, heart and brain; and  $\beta_3$ -adrenoceptors in the human bladder but also have an important role in rodent brown and white fat.

*Clinical uses:*  $\beta$ -Adrenoceptor antagonists are widely used to treat heart failure, arrhythmias, ischaemic heart disease and hypertension (bisoprolol, carvedilol, metoprolol, nebivolol) [830, 831]. labetalol is used in pregnancy to treat hypertension.  $\beta$ -Adrenoceptor antagonists are also used to treat glaucoma (betaxolol, timolol), anxiety, migraine, benign essential tremor, thyrotoxicosis, portal hypertension and variceal bleeding (propranolol for all). Propranolol is the first line treatment for infantile haemangioma, and there is increasing interest in  $\beta$ -adrenoceptor antagonist use to reduce primary growth and metastasis in cancer [330]. Non-selective  $\beta$ -adrenoceptor agonists are used to treat cardiac arrest and anaphylaxis (( $\pm$ )-adrenaline), *via* infusion for shock (( $\pm$ )-adrenaline and noradrenaline), and as a bridge to pacemaker implantation in bradycardia (isoprenaline). Selective  $\beta_2$ -adrenoceptor agonists are used to relieve asthma and COPD (short-acting salbutamol, terbutaline; long-acting salmeterol and formoterol, and ultra-long acting indacaterol, olodaterol and vilanterol) [64].  $\beta_3$ -Adrenoceptor agonists are used to treat overactive bladder syndrome (mirabegron, solabegron and vibegron) [317].

*Antagonists:* High affinity, non-selective  $\beta$ -adrenoceptor antagonists include propranolol, carvedilol, timolol and bupranolol, although for human receptors, all compounds appear to have lower affinity for human  $\beta_3$ -adrenoceptors than for  $\beta_1$ - or  $\beta_2$ -adrenoceptors. Fluorescent analogues of  $\beta$ -ligands *e.g.* CGP 12177 and propranolol can be used to label  $\beta$ -adrenoceptors at the cellular level [57].

[ $^{125}I$ ]ICYP, [ $^3H$ ]CGP12177 and [ $^3H$ ]dihydroalprenolol are high affinity radioligands that label  $\beta_1$ - and  $\beta_2$ -adrenoceptors and at higher concentrations,  $\beta_3$ -adrenoceptors. CGP 20712A and NDD-825 are highly  $\beta_1$ -selective antagonists and ICI 118551 is a  $\beta_2$ -selective antagonist [65].

*Agonists:* isoprenaline and cimaterol are highly efficacious non-selective  $\beta$ -adrenoceptor agonists (relative to  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors). formoterol, salmeterol and vilanterol have high  $\beta_2$ -adrenoceptor selectivity whilst mirabegron, solabegron and vibegron have  $\beta_3$ -adrenoceptor selectivity. L 755507 and L-748337 are partial agonists that display human  $\beta_3$ -adrenoceptor selectivity. [ $^3H$ ]L748337 can be used to selectively label  $\beta_3$ -adrenoceptors in human and rat tissues [790].

*Species differences:* rodent  $\beta_1$  and  $\beta_2$ -adrenoceptors display similar pharmacology to human receptors. There are three  $\beta$ -adrenoceptors in turkey (termed the  $t\beta$ ,  $t\beta_3c$  and  $t\beta_4c$ ) with pharmacology that differs from the human  $\beta$ -adrenoceptors [49]. Significant pharmacological

differences exist between human and mouse  $\beta_3$ -adrenoceptors, which includes mouse splice variants [227] where the isoforms display different signalling characteristics [354].

## Contents

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### Adrenoceptors

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=4>

### Introduction to Adrenoceptors

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=4>

#### Receptors

##### $\alpha_{1A}$ -adrenoceptor

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##### $\alpha_{1B}$ -adrenoceptor

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##### $\beta_3$ -adrenoceptor

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