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Adrenoceptors in GtoPdb v.2023.1

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Abstract

The nomenclature of the Adrenoceptors has been agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [64, 194].

Adrenoceptors, α_1

The three α_1-adrenoceptor subtypes α_{1A}, α_{1B} and α_{1D} are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. -(-)phenylephrine, methoxamine and cirazoline are agonists and prazosin and doxazosin antagonists considered selective for α_1- relative to α_2-adrenoceptors. [^{3}H]prazosin and [^{125}I]HEAT (BE2254) are relatively selective radioligands. S(+)-niguldipine also has high affinity for L-type Ca^{2+} channels. Fluorescent derivatives of prazosin (Bodipy FLprazosin- QAPB) are used to examine cellular localisation of α_1-adrenoceptors. α_1-Adrenoceptor agonists are used as nasal decongestants; antagonists to treat symptoms of benign prostatic hyperplasia (alfuzosin, doxazosin, terazosin, tamsulosin and silodosin, with the last two compounds being $\alpha 1_A$-adrenoceptor selective and claiming to relax bladder neck tone with less hypotension); and to a lesser extent hypertension (doxazosin, terazosin). The α_1- and β_2-adrenoceptor antagonist carvedilol is used to treat congestive heart failure, although the contribution of α_1-adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs are α_1-adrenoceptor antagonists contributing to side effects such as orthostatic hypotension.

Adrenoceptors, α_2

The three α_2-adrenoceptor subtypes α_{2A}, α_{2B} and α_{2C} are activated by (-)-adrenaline and with lower potency by (-)-noradrenaline. brimonidine and talipexole are agonists and rauwolscine and yohimbine antagonists selective for α_2- relative to α_1-adrenoceptors. [^{3}H]rauwolscine, [^{3}H]brimonidine and [^{3}H]RX821002 are relatively selective radioligands. There are species variations in the pharmacology of the α_{2A}-adrenoceptor. Multiple mutations of α_2-adrenoceptors have been described, some associated with alterations in function. Presynaptic α_2-adrenoceptors regulate many functions in the nervous system. The α_2-adrenoceptor agonists

clonidine, guanabenz and brimonidine affect central baroreflex control (hypotension and bradycardia), induce hypnotic effects and analgesia, and modulate seizure activity and platelet aggregation. clonidine is an anti-hypertensive (relatively little used) and counteracts opioid withdrawal. dexmedetomidine (also xylazine) is increasingly used as a sedative and analgesic in human [33] and veterinary medicine and has sympatholytic and anxiolytic properties. The α_2-adrenoceptor antagonist mirtazapine is used as an anti-depressant. The α_{2B} subtype appears to be involved in neurotransmission in the spinal cord and α_{2C} in regulating catecholamine release from adrenal chromaffin cells. Although subtype-selective antagonists have been developed, none are used clinically and they remain experimental tools.

Adrenoceptors, β
The three β-adrenoceptor subtypes β_1, β_2 and β_3 are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Isoprenaline is 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 for β_1- and β_2- relative to β_3-adrenoceptors. (-)-noradrenaline, xamoterol and (-)-Ro 363 show selectivity for β_1- relative to β_2-adrenoceptors. Pharmacological differences exist between human and mouse β_3-adrenoceptors, and the 'rodent selective' agonists BRL 37344 and CL316243 have low efficacy at the human β_3-adrenoceptor whereas CGP 12177 (low potency) and L 755507 activate human β_3-adrenoceptors [88]. β_3-Adrenoceptors are resistant to blockade by propranolol, but can be blocked by high concentrations of bupranolol. SR59230A has reasonably high affinity at β_3-adrenoceptors, but does not discriminate between the three β- subtypes [332] whereas L-748337 is more selective. [^{125}I]-cyanopindolol, [^{125}I]-hydroxy benzylpindolol and [^{3}H]-alprenolol are high affinity radioligands that label β_1- and β_2- adrenoceptors and β_3-adrenoceptors can be labelled with higher concentrations (nM) of [^{125}I]-cyanopindolol together with β_1- and β_2-adrenoceptor antagonists. Fluorescent ligands such as BODIPY-TMR-CGP12177 can be used to track β-adrenoceptors at the cellular level [8]. Somewhat selective β_1-adrenoceptor agonists (denopamine, dobutamine) are used short term to treat cardiogenic shock but, chronically, reduce survival. β_1-Adrenoceptor-preferring antagonists are used to treat cardiac arrhythmias (atenolol, bisoprolol, esmolol) and cardiac failure (metoprolol, nebivolol) but also in combination with other treatments to treat hypertension (atenolol, betaxolol, bisoprolol, metoprolol and nebivolol) [528]. Cardiac failure is also treated with carvedilol that blocks β_1- and β_2-adrenoceptors, as well as α_1-adrenoceptors. Short (salbutamol, terbutaline) and long (formoterol, salmeterol) acting β_2-adrenoceptor-selective agonists are powerful bronchodilators used to treat respiratory disorders. Many first generation β-adrenoceptor antagonists (propranolol) block both β_1- and β_2-adrenoceptors and there are no β_2-adrenoceptor-selective antagonists used therapeutically. The β_3-adrenoceptor agonist mirabegron is used to control overactive bladder syndrome. There is evidence to suggest that β-adrenoceptor antagonists can reduce metastasis in certain types of cancer [197].

Contents

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Adrenoceptors

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

Introduction to Adrenoceptors

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Receptors

α_{1A}-adrenoceptor

https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=22

α_{1B}-adrenoceptor

https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=23

α_{1D}-adrenoceptor

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α_{2A}-adrenoceptor

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α_{2B}-adrenoceptor

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α_{2C}-adrenoceptor

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β_1-adrenoceptor

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β_2-adrenoceptor

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β_3-adrenoceptor

https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=30

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