Adrenoceptors, α_1

Overview: α_1-Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are 7TM receptors activated by the endogenous agonists adrenaline and noradrenaline with equal potency. Phenylephrine, methoxamine and cirazoline are agonists selective for α_1-adrenoceptors relative to α_2-adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are considered selective antagonists for α_1-adrenoceptors relative to α_2-adrenoceptors. [^{3}H]-Prazosin (0.25 nM) and [^{125}I]-HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the α_1-adrenoceptors exist, some of which may display a different spectrum of signalling properties. One polymorphism of the α_{1A}-adrenoceptor has been described but is not associated with disease.

Nomenclature	α_{1A}	α_{1B}	α_{1D}
Other names	α_{1a}, α_{1c}	α_{1b}	$\alpha_{1A/D}$, $\alpha_{1a/d}$
Ensembl ID	ENSG00000120907	ENSG00000170214	ENSG00000171873
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists	A61603, dabuzalgron (Blue *et al.*, 2004)	–	–
Selective antagonists	Tamsulosin (10.5), silodosin (10.4), (+)niguldipine (10.0), SNAP5089 (9.7)	–	BMY7378 (8.4)

The clone originally called the α_{1C}-adrenoceptor corresponds to the pharmacologically defined α_{1A}-adrenoceptor (see Ford *et al.*, 1994; Hieble *et al.*, 1995). Some tissues possess α_{1A}-adrenoceptors that display relatively low affinity in functional and binding assays for prazosin ($pK_i < 9$) that might represent different receptor states (termed α_{1L}-adrenoceptors, Ford *et al.*, 1997; Morishima *et al.*, 2007). α_{1A}-Adrenoceptor C-terminal splice variants form homo- and heterodimers, but fail to generate a functional α_{1L}-adrenoceptor (Ramsay *et al.*, 2004). α_{1D}-Adrenoceptors form heterodimers with α_{1B}- or β_2-adrenoceptors that show increased cell-surface expression (Uberti *et al.*, 2005). Heterodimers formed between α_{1D}- and α_{1B}-adrenoceptors have distinct functional properties (Hague *et al.*, 2004). α_{1D}-Adrenoceptors are mainly located intracellularly. (+)Niguldipine also has high affinity for L-type Ca^{2+} channels.

Signalling is predominantly via $G_{q/11}$ but α_1-adrenoceptors also couple to $G_{i/o}$, G_s, $G_{12/13}$ and G_h. There are differences between subtypes in coupling efficiency to different pathways – for example coupling efficiency to Ca^{2+} signalling is $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$, but for MAP kinase signalling is $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$. The subtypes also seem to show differences in regulation.

Abbreviations: **A61603**, *N*-(5-[4,5-dihydro-1*H*-imidazol-2-y]-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide hydrobromide; **BMY7378**, 8-(2-[4-{2methoxyphenyl}-1-piperazinyl]ethyl)-8-azaspiro[4,5]decane-7,9-dione dihydrochloride; **HEAT**, 2-*β*-4-hydroxy-3-iodophenylethylaminomethyltetralone; **RS17053**, *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-*α*,*α*-dimethyl-1*H*-indole-3-ethanamide; **silodosin**, (-)-(*R*)-1-(3-hydroxypropyl)-5-(2-[2-{2-(2,2,2-trifluoroethoxy)phenoxyl}ethylamino]propyl)indoline-7-carboxamide, also known as KMD3213; **SNAP5089**, 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate-*N*-[3-(4,4-diphenylpiperidin-1-yl) propyl]amide methyl ester; **SNAP5272**, 5-carboxamide-2,6-diethyl-1,4-dihydro-3-[*N*-(3-[4-hydroxy-4-phenylpiperidinyl]propyl)]carboxamido-4-(4-nitrophenyl)

Further Reading

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