Adrenoceptors, $\alpha_1$

**Overview:** $\alpha_1$-Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund et al., 1994) are GPCR activated by the endogenous agonists adrenaline and noradrenaline with equal potency. Phenylephrine, methoxamine and cirazoline are agonists selective for $\alpha_1$-adrenoceptors relative to $\alpha_2$-adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are antagonists considered selective for $\alpha_1$-adrenoceptors relative to $\alpha_2$-adrenoceptors. $[^{3}H]$-Prazosin (0.25 nM) and $[^{3}H]$-HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the $\alpha_1$-adrenoceptors exist, some of which may display a different spectrum of signalling properties. One polymorphism of the $\alpha_1$-adrenoceptor has been described but is not associated with disease.

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>$\alpha_{1A}$</th>
<th>$\alpha_{1B}$</th>
<th>$\alpha_{1D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>$\alpha_{1A}$, $\alpha_{1A}$</td>
<td>$\alpha_{1B}$</td>
<td>$\alpha_{1AD}$, $\alpha_{1AD}$</td>
</tr>
<tr>
<td>Ensembl ID</td>
<td>ENSG00000120907</td>
<td>ENSG00000170214</td>
<td>ENSG00000171873</td>
</tr>
<tr>
<td>Principal transduction</td>
<td>$G_q$</td>
<td>$G_q$</td>
<td>$G_q$</td>
</tr>
<tr>
<td>Selective agonists</td>
<td>A61603, dabuzalgron (Blue et al., 2004)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>Tamsulosin (10.5), silodosin (10.4), (+)-niguldipine (10.0), SNAP5089 (9.7)</td>
<td>–</td>
<td>BMY7378 (8.4)</td>
</tr>
</tbody>
</table>

The clone originally called the $\alpha_{1C}$-adrenoceptor corresponds to the pharmacologically defined $\alpha_{1A}$-adrenoceptor (see Hieble et al., 1995). Some tissues possess $\alpha_{1A}$-adrenoceptors that display relatively low affinity in functional and binding assays for prazosin ($pK_i < 9$) that might represent different receptor states (termed $\alpha_{1A}$-adrenoceptors, Ford et al., 1997; Morishima et al., 2007). $\alpha_{1A}$-Adrenoceptor C-terminal splice variants form homo and heterodimers, but fail to generate a functional $\alpha_{1A}$-adrenoceptor (Ramsay et al., 2004). Recent studies suggest that the $\alpha_{1A}$-adrenoceptor phenotype may result from the interaction of $\alpha_{1A}$-adrenoceptors with cysteine-rich epidermal growth factor-like domain 1a (CRELD1a) (Nishimune et al., 2010). $\alpha_{1A}$-Adrenoceptors form heterodimers with $\alpha_{1D}$- or $\beta_2$-adrenoceptors that show increased cell-surface expression (Uberti et al., 2005). Heterodimers formed between $\alpha_{1A}$- and $\alpha_{1D}$-adrenoceptors have distinct functional properties (Hague et al., 2004). $\alpha_{1D}$-Adrenoceptors are mainly located intracellularly. (+)-Niguldipine also has high affinity for L-type Ca$^{2+}$ channels.

Signalling is predominantly via $G_q$ but $\alpha_1$-adrenoceptors also couple to $G_{12/13}$. Several ligands activating $\alpha_1$-adrenoceptors display ligand directed signalling bias. For example, oxymetazoline is a full agonist for extracellular acidification rate (ECAR) and a partial agonist for Ca$^{2+}$ release but does not stimulate cAMP production. Phenylephrine is biased toward ECAR versus Ca$^{2+}$ release or cAMP accumulation but not between Ca$^{2+}$ release and cAMP accumulation (Evans et al., 2011). There are also differences between subtypes in coupling efficiency to different pathways – e.g. 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-1H-imidazol-2-yl]-2-hydroxy-5,6,7,8-tetrahydrodiphenyl-1-yl)methanesulfonyl amide hydrobromide; BMY7378, 8-(2-[[4-[(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decan-7-nine dihydrochloride; HEAT, 2-b-4-hydroxy-3-iopophenylethylaminomethyltetralone; S17053, N-[2-(2-cyclopropylmethoxymethyl)ethyl]-5-chloro-a,a-dimethyl-1H-indole-3-ethanamide; silodosin, (R)-(R)-1-(3-hydroxypropyl)-5-(2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)ethylaminopropyl)methyl-7-carboxamide, also known as KMD3213; SNAP5089, 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropridine-3,5-dicarboxylate-N-[3-(4,4-diphenylpiperidin-1-yl)propyl]amide methyl ester

**Further Reading**


References


(Source: BRITISH JOURNAL OF PHARMACOLOGY)