

α_2 -Adrenoceptors

Key References

- Bailey, S.R., et al., Rho kinase mediates cold-induced constriction of cutaneous arteries: role of α_{2c} -adrenoceptor translocation., *Circ. Res.*, **94**, 1367-1374 (2004).
- Bylund, D.B., et al., Pharmacological characteristics of alpha 2-adrenergic receptors: Comparison of pharmacologically defined subtypes with subtypes identified by molecular cloning., *Mol. Pharmacol.*, **42**, 1-5 (1992).
- Bylund, D.B., et al., "Adrenoceptors." in: The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edition, pp. 88-103, IUPHAR Media, London, UK (2000).
- Chotani, M.A., et al., Silent α_{2c} adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries., *Am. J. Physiol.*, **278**, H1075-1083 (2000).
- Hein, I., et al., Two functionally distinct α_2 -adrenergic receptors regulate sympathetic neurotransmission., *Nature*, **402**, 181-184 (1999).
- Hieble, J.P., Ruffolo, R.R., Jr., Subclassification and nomenclature of α_1 - and α_2 -adrenoceptors. in Progress in Drug Research, Ed. E. Jucker, pp. 81-130 Birkhauser Verlag (1996).
- Hieble, J.P., et al., Alpha and beta-adrenoceptors: From the gene to the clinic. Part I., *J. Med. Chem.*, **38**, 3415-3444 (1995).
- Hudson, A.L., et al., *In vitro* and *in vivo* approaches to characterization of the alpha2-adrenoceptor." *J. Auton. Pharmacol.*, **19**, 311-320 (1999).
- Kamibayashi, T., Maze, M., Clinical uses of alpha2-adrenergic agonists. *Anesthes.*, **93**, 1345-1349 (2000).
- Puolivali, J., et al., Alpha α_{2c} -adrenoceptor mediated regulation of cortical EEG arousal., *Neuropharmacol.*, **43**, 1305-1312 (2002).
- Ruffolo, R.R., Jr., et al., Alpha- and beta- adrenoceptors: From the gene to the clinic. Part 2., *J. Med. Chem.*, **38**, 3681-3716 (1995).
- Trendelenburg, A.U., et al., All three alpha2-adrenoceptor types serve as autoreceptors in postganglionic sympathetic neurons., *Naunyn-Schmiedeberg Arch. Pharmacol.*, **368**, 504-512 (2003).

Overview

α_2 -Adrenoceptors are widely distributed and are activated by norepinephrine, released from sympathetic nerve terminals or by epinephrine, released from the adrenal medulla and from some neurons in the CNS. Perhaps the most extensively characterized action is the prejunctionally mediated inhibition of the release of neurotransmitter from many peripheral and central neurons. Activation of prejunctional autoreceptors on sympathetic neurons results in a sympatholytic action. α_2 -Adrenoceptors are also present at postjunctional sites, where they mediate actions such as smooth muscle contraction, platelet aggregation and inhibition of insulin secretion. Activation of postsynaptic α_2 -adrenoceptors in the brainstem results in an inhibition of sympathetic outflow to the periphery. Many α_2 -adrenoceptor mediated effects are mediated via inhibition of adenylyl cyclase as a consequence of interaction of the agonist-receptor complex with G_i , although other second messengers remain to be characterized.

Three α_2 -adrenoceptor proteins have been cloned. These recombinant receptors, designated as α_{2a} , α_{2b} and α_{2c} , result in four discrete pharmacological profiles, since the α_{2a} adrenoceptor appears to exist as species orthologs, with those of human, pig and rabbit having a profile designated as α_{2a} , while those of rat, mouse, guinea-pig and cow exhibit pharmacology designated as α_{2d} , α_{2a} and α_{2d} mediated responses can be differentiated by the low sensitivity of the α_{2d} adrenoceptor to blockade by the commonly used antagonists yohimbine and rauwolscine.

The α_{2a} or α_{2d} subtype (depending on species) appears to be responsible for most α_2 -adrenoceptor mediated responses. This

includes the major component of prejunctional modulation of sympathetic neurotransmission and central sympatho-inhibitory activity, although all three subtypes may contribute. Gene knockout experiments support this premise, but show that, at least in mice, the initial pressor action of an α_2 -adrenoceptor agonist results from activation of the α_{2b} adrenoceptor. While knockout of the α_{2c} adrenoceptor has no apparent cardiovascular effects, elimination of both α_{2a} and α_{2c} adrenoceptors results in complete loss of prejunctional modulation of adrenergic neurotransmission and induces pathologic effects related to excess adrenergic tone. The α_{2c} adrenoceptor mediates cold-induced augmentation of α -adrenoceptor induced vasoconstriction, which may involve translocation of receptors from intracellular sites to the plasma membrane. Overexpression and knockout experiments suggest that the α_{2c} adrenoceptor may have important functions in the CNS.

Selective α_2 -adrenoceptor agonists are used for the treatment of hypertension; their sedative and analgesic activity has also led to their use as adjuncts to general anesthesia. Other applications for central α_2 -adrenoceptor activation include opiate withdrawal, attention deficit hyperactivity disorder and Tourette's syndrome. Intra-ocular administration of an α_2 -adrenoceptor agonist will reduce intra-ocular pressure in glaucoma. None of the agonists employed clinically show pharmacologically significant selectivity between the α_2 -adrenoceptor subtypes.

α_2 -Adrenoceptors

CURRENTLY ACCEPTED NAME	α_{2A} (A213)	α_{2B}	α_{2C} (A214)	α_{2D}
ALTERNATE NAME	—	—	—	α_{2A}^a
STRUCTURAL INFORMATION	450 aa (human)	451 aa (human)	461 aa (human)	450 aa (rat)
SUBTYPE SELECTIVE AGONIST	Oxymetazoline (partial) (O2378)	Not known	Not known	Not known
SUBTYPE SELECTIVE ANTAGONISTS	BRL 44408 (B4559)	Prazosin (P7791), ARC 239, Imiloxan Rauwolscine (R104)	Prazosin (P7791), ARC 239, MK-912 (M7065),	BRL 44408 (B4559)
RECEPTOR SELECTIVE AGONISTS	UK 14,304 (U104), Guanabenz (G110), p-Aminoclonidine (A0779), B-HT 920 (B162), B-HT 933 (B161)	UK 14,304 (U104), Guanabenz (G110), p-Aminoclonidine (A0779), B-HT 920 (B162), B-HT 933 (B161)	UK 14,304 (U104), Guanabenz (G110), p-Aminoclonidine (A0779), B-HT 920 (B162), B-HT 933 (B161)	UK 14,304 (U104), Guanabenz (G110), p-Aminoclonidine (A0779), B-HT 920 (B162), B-HT 933 (B161)
RECEPTOR SELECTIVE ANTAGONISTS	RX 821002 (R9525), Yohimbine (Y3125), SKF-86466 (S1563), MK-912 (M7065)	RX 821002 (R9525), Yohimbine (Y3125), SKF-86466 (S1563), MK-912 (M7065)	RX 821002 (R9525), Yohimbine (Y3125), SKF-86466 (S1563), MK-912 (M7065)	RX 821002 (R9525), Yohimbine (Y3125), SKF-86466 (S1563), MK-912 (M7065)
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)
RADIOLIGANDS OF CHOICE	[³ H]-Rauwolscine [³ H]-RX 821002	[³ H]-Rauwolscine [³ H]-RX 821002	[³ H]-Rauwolscine [³ H]-RX 821002 [³ H]-MK-912	[³ H]-RX 821002
TISSUE EXPRESSION	CNS, lung, blood vessels, skeletal muscle	Thalamus, lung, kidney	CNS, lung	Aorta, spleen (rat)
PHYSIOLOGICAL FUNCTION	Inhibition of neurotransmission, vasoconstriction	Smooth muscle contraction, thermoregulation	Modulation of neurotransmission, vasoconstriction	Inhibition of neurotransmission
DISEASE RELEVANCE	Attention Deficit Disorder?	Not known	Raynaud's disease	Not known

Abbreviations

ARC 239: (2-[2-[4-(o-Methoxyphenyl)piperazin-1-yl]ethyl]-4,4-dimethyl-1,3-(2H,4H)-isoquinolinedione

BHT 920: 5,6,7,8-Tetrahydro-6-(2-propenyl)-4H-thiazolo[4,5-d]azepine-2-amine

BHT 933: 6-Ethyl-5,6,7,8-tetrahydro-4H-oxazolo[4,5-d]azepin-2-amine

BRL 44408: (2-[2H-(1-Methyl-1,3-dihydroisoindole)methyl]-4,5-dihydroimidazole

MK-912: ((2S,12bS)1',3'-Dimethylspiro(1,3,4,5',6,6',7,12b-octahydro-2H-benzol[b]furo[2,3-a]quinazoline)-2,4'-pyrimidin-2'-one

RX 821002: 2-Methoxy-idazoxan

SKF-86466: 6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine

UK 14,304: 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine

FOOTNOTES

^a The α_{2A} and α_{2D} are pharmacologically distinct, but are genetic orthologs. The α_{2A} is found in the human, pig and rabbit, whereas the α_{2D} is found in the rat, mouse and cow.