

α_1 -Adrenoceptors

Key References

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Overview

α_1 -Adrenoceptors are widely distributed, and are activated either by norepinephrine released from sympathetic nerve terminals or by epinephrine released from the adrenal medulla. Receptor activation mediates a variety of functions, including contraction of smooth muscle, cardiac stimulation, cellular proliferation/apoptosis and activation of hepatic gluconeogenesis and glycogenolysis. α_1 -Adrenoceptors are also widely distributed within the CNS, where their activation generally results in depolarization and increased neuronal firing rate. Most of the peripheral actions of α_1 -adrenoceptors are mediated through phosphatidylinositol turnover, while there is evidence for activation of adenylyl cyclase within the CNS.

Three distinct α_1 -adrenoceptor proteins have been cloned; after some confusion in nomenclature, it has now been established that these three recombinant α_1 -adrenoceptors, designated as α_{1a} , α_{1b} and α_{1d} correspond to the pharmacologically defined α_{1a} , α_{1b} , and α_{1d} adrenoceptors in native tissues. Multiple splice variants of the α_{1a} adrenoceptor have been identified; however they appear to have identical pharmacological characteristics. The α_1 -adrenoceptor mediating contraction of several vascular and urogenital tissues has distinct pharmacology from the other 3 subtypes, and has been designated as the α_{11} adrenoceptor. This receptor has not been cloned; it now appears that the α_{11} adrenoceptor represents a discrete affinity state of the α_{1a} adrenoceptor.

The subcellular location of expressed recombinant α_1 -adrenoceptors may be subtype dependent. Chloroethylclonidine, commonly used as a selective α_{1b} antagonist for receptor subclassification, may be able to alkylate all α_1 -adrenoceptors, with

its apparent selectivity for α_{1b} versus α_{1a} adrenoceptors, at least in cells expressing recombinant receptors, due to accessibility only to the α_{1b} receptor. Recent evidence shows that it may be possible to design peptides which can selectively antagonize α_1 -adrenoceptor subtypes.

In most cases, the particular subtype involved in an α_1 -adrenoceptor mediated response has not yet been identified. This is due in part to the lack of subtype selective antagonists suitable for *in vivo* evaluation. Depending on the species and/or vascular bed, each α_1 -adrenoceptor subtype can contribute to vascular contraction. For example, contraction of the rat caudal artery is mediated by the α_{1a} adrenoceptor, canine aorta by the α_{1b} and rat aorta by the α_{1d} adrenoceptor. The response to α_1 -adrenoceptor stimulation in many canine and human vessels has α_{11} pharmacology. Knockout of either the α_{1a} , α_{1b} or α_{1d} adrenoceptor significantly attenuates the pressor response to α_1 -adrenoceptor activation in the mouse. Contraction of prostatic and urethral smooth muscle appears to be mediated by the α_{11} adrenoceptor. α_1 -Adrenoceptor antagonists having selective affinity for α_{1a} and α_{11} adrenoceptors, as well as antagonists having affinity for both α_{1a} and α_{1d} adrenoceptors, have been evaluated clinically for the treatment of benign prostatic hyperplasia. However, it appears that these drugs are not superior to the non-subtype selective α_1 -adrenoceptor antagonists which have been proven to be effective for this indication.

α_1 -Adrenoceptors

CURRENTLY ACCEPTED NAME	α_{1A}	α_{1B}	α_{1D}
ALTERNATE NAME ^a	α_{1a} , α_{1c}	α_{1b}	α_{1d} , $\alpha_{1a/d}$
STRUCTURAL INFORMATION	466 aa (human)	517 aa (human)	572 aa (human)
SUBTYPE SELECTIVE AGONISTS	SKF-89748, A-61603	Not known	Not known
SUBTYPE SELECTIVE ANTAGONISTS	(+)-Niguldipine (N135), 5-Methylurapidil (U101), Ro-70-0004, RS-17053	(±)-Cyclazosin (C247), L-765,314 (L3040)	BMY 7378 (B134)
RECEPTOR SELECTIVE AGONISTS	Cirazoline (C223), Methoxamine (M6524), Phenylephrine (P6126)	Phenylephrine (P6126)	Methoxamine (M6524), Phenylephrine (P6126)
RECEPTOR SELECTIVE ANTAGONISTS	Corynanthine (C3380), Prazosin (P7791)	Corynanthine (C3380), Prazosin (P7791)	Corynanthine (C3380), Prazosin (P7791)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-Prazosin, [¹²⁵ I]-HEAT, [¹²⁵ I]-L-762,459	[³ H]-Prazosin, [¹²⁵ I]-HEAT	[³ H]-Prazosin, [¹²⁵ I]-HEAT
TISSUE EXPRESSION	Heart, liver, CNS, urogenital smooth muscle	Resistance vessels, spleen, kidney	Aorta, bladder, CNS
PHYSIOLOGICAL FUNCTION	Smooth muscle contraction, myocyte hypertrophy	Smooth muscle contraction, CNS stimulation	Smooth muscle contraction, locomotor activity
DISEASE RELEVANCE	BPH, stress incontinence	Not known	Overactive bladder?

Abbreviations

A-61603: N-[5-(4,5-Dihydro-1H-imidazol-2-yl)-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide hydrobromide

BMY 7378: 8-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione

HEAT: 2-(β-4-Hydroxyphenyl)ethylaminomethyltetralone

L-762,459: (±)-1-(3-[[5-Carbamoyl-2-{2-[(4-hydroxy-3-iodobenzimidoyl)-amino]-ethoxy-methyl]-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-4-carboxylic acid methyl ester

L-765,314: 4-Amino-2-[4-[1-(benzyloxycarbonyl)-2(S)-[[1,1-dimethylethyl)amino]carbonyl]-piperazinyl]-6,7-dimethoxyquinazoline

RS-17053: (N-[2-(2-Cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α,α-dimethyl-1H-indole-3-ethanamine

SKF-89748: 1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine

FOOTNOTES

^a Recombinant receptors designated by lower case subscripts