

β -Adrenoceptors

Key References

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Overview

β -Adrenoceptors are widely distributed, found at both central and peripheral sites, and are activated either via norepinephrine released from sympathetic terminals or via epinephrine released from the adrenal medulla. Important physiological consequences of β -adrenoceptor activation include stimulation of cardiac rate and force, relaxation of vascular, urogenital and bronchial smooth muscle, stimulation of renin secretion from the juxta-glomerular apparatus, stimulation of insulin and glucagon secretion from the endocrine pancreas, stimulation of glycogenolysis in liver and skeletal muscle and stimulation of lipolysis in the adipocyte. Prejunctional β -adrenoceptors are present on some central and peripheral nerve terminals, where their activation results in facilitation of stimulation-evoked neurotransmitter release. However, in contrast to the prejunctional α 2-adrenoceptors, these prejunctional receptors do not appear to have major physiologic significance. Most β -adrenoceptor mediated actions involve stimulation of adenylyl cyclase via interaction of the agonist-receptor complex with G_s .

Three β -adrenoceptor proteins have been cloned, and the characteristics of these recombinant receptors correspond with those of the three well characterized β -adrenoceptors on native tissues, designated as β_1 , β_2 and β_3 . Species differences appear to be important for the β_3 -adrenoceptor, since several selective β_3 -adrenoceptor agonists can activate rodent, but not human β_3 -adrenoceptors. There appear to be multiple affinity states of the β_1 -adrenoceptor, which may explain the distinct pharmacology of a β -adrenoceptor mediating cardiac contractility.

Many useful pharmacological tools are available for β -adrenoceptor characterization. These include agonists capable of selectively

activating β_1 -, β_2 - or β_3 -adrenoceptors, as well as antagonists selective for each of the three subtypes. While it was initially thought that cardiac stimulation involved primarily the β_1 -adrenoceptor, it now appears that all of the receptor subtypes may be involved. Bronchodilation appears to be mediated primarily by the β_2 -adrenoceptor. The β_3 -adrenoceptor is responsible for lipolysis in white adipose tissue and thermogenesis in the brown adipose tissue found in rodents. Renin release appears to be mediated by the β_1 -adrenoceptor.

β_2 -Adrenoceptor agonists are commonly used as bronchodilators. Selective β_3 -adrenoceptor agonists are being developed for the treatment of type II diabetes, obesity and overactive bladder. β -Adrenoceptor antagonists, either non subtype-selective or selective for the β_1 -adrenoceptor, are widely used as antihypertensives, although the mechanism for this action is still not clearly understood. Intra-ocular administration of nonselective β -adrenoceptor antagonists is a common treatment for glaucoma. Carvedilol, a molecule combining nonselective β -adrenoceptor blockade with α_1 -adrenoceptor blockade, has recently been shown to produce a dramatic reduction in the mortality/morbidity associated with congestive heart failure.

β-Adrenoceptors

CURRENTLY ACCEPTED NAME	β ₁ (B143)	β ₂ (B144)	β ₃
ALTERNATE NAME	—	—	atypical β
STRUCTURAL INFORMATION	477 aa (human)	413 aa (human)	408 aa (human)
SUBTYPE SELECTIVE AGONISTS	Norepinephrine (A7257), Xamoterol (X3253), Denopamine (D7815), T-0509	Procaterol (P9180), Salbutamol (S8260, S5013), Fenoterol (F1016)	BRL 37344 (B169), CL 316243 (C5976), SB-226552
SUBTYPE SELECTIVE ANTAGONISTS	CGP20712A (C231), Betaxolol (B5683), Atenolol (A7655)	ICI-118,551 (I127), Butoxamine (B1385), α-Methylpropranolol	SR 58894, SR 59230A (S8688)
RECEPTOR SELECTIVE AGONIST	Isoproterenol (I5627)	Isoproterenol (I5627),	Isoproterenol (I5627)
RECEPTOR SELECTIVE ANTAGONISTS	Alprenolol (A8676), Propranolol (P0884, P8688), Pindolol (P0778)	Alprenolol (A8676), Propranolol (P0884, P8688), Pindolol (P0778)	Bupranolol, Cyanopindolol (C238)
SIGNAL TRANSDUCTION MECHANISMS	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP)
RADIOLIGAND OF CHOICE	[¹²⁵ I]-I-ICYP	[¹²⁵ I]-I-ICYP	[¹²⁵ I]-I-ICYP
TISSUE EXPRESSION	Coronary artery, kidney, heart, CNS	Kidney, lung, heart, CNS	Adipose tissue, GI tract vascular endothelium
PHYSIOLOGICAL FUNCTION	Cardiac stimulation, coronary vasodilation	Smooth muscle relaxation	Adipocyte lipolysis, bladder relaxation, thermogenesis
DISEASE RELEVANCE	Hypertension, congestive heart failure	Asthma?	Obesity, diabetes

Abbreviations

BRL 37344: (±)-(R*,R*)-4-[2-((2-(3-Chlorophenyl)-2-hydroxyethyl)amino)propyl]phenoxy)acetic acid

CGP20712A: (±)-2-Hydroxy-5-[2-[[2-hydroxy-3-[4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]]phenoxy]propyl]-amino]ethoxy]-benzamide methanesulfonate

CL 316243: (R,R)-5-[2-[[2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-propyl]1,3-benzodioxole-2,2-dicarboxylate

ICI-118,551: (±)-1-[2,3-(Dihydro-7-methyl-1H-inden-4-yl)oxy]-3-[(1-methylethyl)amino]-2-butanol

ICYP: lodocyanopindolol

SB-226552: (S)-4-[2-[2-Hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl]phenoxy)methylcyclohexylphosphinic acid

SR 58894: 3-(2-Allylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronaphth-1-ylamino]-(2S)-2-propanol hydrochloride

SR 59230: 3-(2-Ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronaphth-1-ylamino]-(2S)-2-propanol oxalate

T-0509: [(–)-(R)-1-(3,4-Dihydroxyphenyl)-2-[(3,4-dimethoxyphenethyl)-amino]ethanol

FOOTNOTES