

Angiotensin Receptors

Key References

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Overview

Different receptors/binding sites have been identified for the biologically active angiotensin (Ang) peptides, i.e. Ang II (1-8), Ang III (2-8), Ang IV (3-8) and Ang (1-7), based on the availability of selective agonists and antagonists, signal transduction mechanisms and structure of the receptor proteins. The primary receptors for Ang II (and Ang III) are designated AT₁ and AT₂. AT₁ receptors exhibit high affinity for the biphenyltetrazole class of non-peptide antagonists. These clinically used angiotensin receptor blockers (ARB's) are generically known as sartans. Tetrahydroimidazole-pyridines behave as selective non-peptide AT₂ receptor antagonists. The octapeptide Ang II receptor antagonist, saralasin, [Sar¹,Ala⁸]-Ang II and other 8 position aliphatic amino acid substituted Ang II analogs, do not discriminate between AT₁ and AT₂ receptors. On the other hand, the antagonist [Sar¹,Gly⁸] Ang II shows moderate selectivity for the AT₁ receptor. The peptides CGP 42112A and p-Aminophenylalanine Ang II bind selectively to the AT₂ receptor, and exhibit agonist activity.

The sequence identity between the AT₁ (359 aa) and AT₂ (363 aa) receptors is only 34%, but both receptors belong to the G protein-coupled receptor superfamily. In humans, the single gene encoding the AT₁ receptor protein is found on chromosome 3. Two subtypes, AT_{1A} and AT_{1B}, exhibiting a 94% overall sequence identity, are found in rodents. In the rat, the AT_{1A} and AT_{1B} receptor genes are located on chromosomes 17 and 2, respectively. In the mouse the genes are located on chromosomes 13 and 3, respectively. Upon stimulation, the AT₁ receptor couples via G protein- (predominantly G_{q/11}) dependent and independent mechanisms, modulating several intracellular signaling mechanisms involv-

ing phospholipases C, D and A₂, adenylyl cyclase, Erk MAP kinase, c-Jun N-Terminal kinase (JNK) and the Jak/STAT pathway, some of which involve transactivation of the EGF receptor. Mouse, rat and human AT₂ receptor genes have been mapped to the X-chromosome and no subtypes or splice variants have been described. The AT₂ receptor also couples via G protein- (G_i) dependent and independent mechanisms. These include activating tyrosine phosphatases (MKP1 and SHP-1) and serine/threonine phosphatases to decrease in MAP kinase activity, activation of PLA₂, opening of delayed-rectifier potassium channels and closing of T-type calcium channels, and stimulation of ceramide production.

The predominant role of the AT₁ receptor in mediating the pathophysiological actions of Ang II underlies the effectiveness of AT₁ receptor antagonists to lower arterial blood pressure, reduce cardiac pre- and afterload, inhibit sympathetic activity, promote salt and water excretion, and prevent cardiovascular hypertrophy, cardiac failure and atherosclerosis mediated by activation of the renin-angiotensin system. The functional role(s) of the AT₂ receptor remain(s) incompletely understood, but reports indicate vasodilatory, natriuretic, antiproliferative/antihypertrophic, apoptotic, cardioprotective and possibly cerebroprotective actions of Ang II via this site. A consistent theme is that stimulation of AT₂ receptors produces opposite effects to those mediated by AT₁ receptors. Since AT₁ receptors exert feedback inhibition on Ang II formation, selective AT₁ receptor blockade will increase circulating Ang II in the bloodstream leading to increased AT₂ receptor stimulation, which (via a vasodilatory action) may contribute to the beneficial actions of ARBs. The 3-8 hexapeptide Ang IV binds to a

site that is distinct from the AT₁ and AT₂ receptors, designated as the AT₄ receptor. This site has high affinity for Ang IV and the structurally unrelated decapeptide LVV-Hemorphin-7 (LVV-H7), and much lower affinity for Ang II and AT₁/AT₂ receptor-selective ligands. The AT₄ receptor has been identified as the transmembrane enzyme insulin-regulated membrane aminopeptidase (IRAP), and Ang IV, LVV-H7 and other AT₄ receptor-selective ligands inhibit IRAP catalytic activity. The major described function of Ang IV is facilitation of memory retention and retrieval.

Ang (1-7) can be formed directly from Ang I by the action of neutral- or prolyl-endo-peptidases, or from Ang II via angiotensin converting enzyme-2 (ACE-2). The major described actions of Ang (1-7) are vasodilation, via stimulation of nitric oxide, prostaglandins and potentiation of bradykinin actions, and antidiuresis. These effects are abolished by the specific Ang (1-7) antagonist [D-Ala⁷]-Ang (1-7), which has little effect at AT₁ or AT₂ receptors. While an Ang (1-7) receptor has not been cloned, evidence indicates that it is an endogenous ligand for the G protein-coupled receptor Mas.

Angiotensin Receptors

CURRENTLY ACCEPTED NAME	AT ₁ ^a	AT ₂ (A8602)
STRUCTURAL INFORMATION^b	359 aa (human)	363 aa (human)
RECEPTOR AGONISTS (PEPTIDE)	Ang II (A9525) > Ang III (I0385)	Ang II (A9525) = Ang III (I0385), CGP42112A (C160), p-aminophenylalanine ⁶ Ang II
RECEPTOR AGONISTS (NON-PEPTIDE)	L-162,313 (L1415), L-163,491	Not known
RECEPTOR ANTAGONISTS (PEPTIDE)	Sar ¹ ,Ile ⁸ Ang II (A8776), Saralasin (A2275), Sar ¹ ,Gly ⁸ Ang II (A7401)	Sar ¹ ,Ile ⁸ Ang II (A8776), Saralasin (A2275)
RECEPTOR ANTAGONISTS (NON-PEPTIDE)	DuP 753 (Losartan), EXP3174 (active metabolite of Losartan), SKF-108566 (Eprosartan), TCV-116 (Candesartan), L-158,809, SR 47436 (Irbesartan), CGP48933 (Valsartan), BIBR277 (Telmisartan) (T8949), CS-866 (Olmesartan)	PD 123,177, PD 123,319 (P186), PD 126,055, EXP801, L-159,686, L-161,638
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG), G _i (Adenylyl cyclase inhibition), increase Erk MAP kinase and JNK activities, increase Jak/STAT activity, transactivation of EGF receptor	G _i (Adenylyl cyclase inhibition), Activate Tyr and Ser/Thr phosphatases, decrease in Erk MAP kinase, increase ceramide, activate PLA ₂
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-[Sar ¹ ,Ile ⁸]-Ang II [³ H]-L-158,809	[¹²⁵ I]-[Sar ¹ ,Ile ⁸]-Ang II [¹²⁵ I]-CGP42112A
TISSUE EXPRESSION	Vascular smooth muscle, liver, kidney, heart, lung, adrenal cortex and medulla, brain, pituitary	Most fetal tissues, adult tissues, kidney, heart, mesenteric vessels, adrenal cortex and medulla, brain, uterus, ovary (atretic follicles)
PHYSIOLOGICAL FUNCTION	Vasoconstriction, aldosterone secretion, sodium and water retention, vasopressin secretion, sympathetic facilitation, water and sodium intake, cell growth, cell proliferation	Vasodilation, natriuresis, anti-proliferation, anti-hypertrophy, anti-fibrosis, cardioprotection, development, cerebroprotection?
DISEASE RELEVANCE	Hypertension, cardiac hypertrophy, heart failure, kidney failure, atherosclerosis	Not known

Abbreviations

BIBR277: 4'-[(1,4'-Dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid
CGP42112A: Nicotinic acid-Tyr-N-benzoxyl-carbonyl-Arg-Lys-His-Pro-Ile-OH
CGP48933: N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine
CS-866: 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester
E3174: 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid
EXP801: 2-(Diphenylacetyl)-6-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
L-158,809: 5,7-Dimethyl-2-ethyl-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-3H-imidazo[4,5-b]pyridine
L-159,686: 1,4-Bis-diphenylcarbonyl-piperazine-2-carboxylic acid
L-161,638: 2-Ethyl-6-[N-benzyl-N-(2-thienoyl)amino-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]quinazolin-4-(3H)-one

L-162,313: 5,7-Dimethyl-2-ethyl-3-[[4-[2-(n-butylloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]imidazo[4,5,6]pyridine
L-163,491: 5,7-Dimethyl-2-ethyl-3-[[2'-((butylloxycarbonyl)aminosulfonyl)-5'-(3-methoxybenzyl)-[1,1'-biphenyl]-4-yl]methyl]-3H-imidazo[4,5-b]pyridine
PD 123,177: S(+)-1-[(4-Amino-3-methylphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo-(4,5-c)pyridine-6-carboxylic acid
PD 123,319: S(+)-1-[[4-Dimethylamino]-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxylic acid
PD 126,055: 2-(Diphenylacetyl)-5-benzyloxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid
SKF 108566: (aE)-a-[[2-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene]-2-thiophenepropanoic acid
SR 47436: 2-Butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one
TCV 116: 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid 1-[[cyclohexyloxy]carbonyloxy]ethyl ester

FOOTNOTES

- a** Further subtypes of rat and mouse AT₁ receptors, designated AT_{1A} and AT_{1B}, have been cloned and sequenced. In the human, only one AT₁ receptor gene has been identified.
b "Atypical" AT receptors: 362/363 aa (amphibian), 359 aa (chicken), 359 aa (turkey) and 359 aa (gerbil) have also been cloned.