

Angiotensin Receptors

Key References

- Bottari, S.P. et al. "Angiotensin II receptor subtypes: Characterization, signaling mechanisms, and possible physiological implications." *Front. Neuroendocrinol.* **14**, 123-171 (1993).
- Carey, R.M. et al. "Role of the angiotensin type 2 receptor in the regulation of blood pressure and renal function." *Hypertension* **35**, 155-163 (2000).
- Conlin, P.R. et al. "Angiotensin II antagonists for hypertension: Are there differences in efficacy?" *Am. J. Hypertens.* **13**, 418-426 (2000).
- de Gasparo, M. et al. "Angiotensin receptors." in: *The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edition*, pp. 115-123, IUPHAR Media, London, UK (2000).
- de Gasparo, M. et al. "International Union of Pharmacology. XXIII. The angiotensin II receptors." *Pharmacol. Rev.* **52**, 415-472 (2000).
- Dinh, D.T. et al. "Angiotensin receptors: distribution, signalling and function." *Clin. Sci. (Colch)* **100**, 481-492 (2001).
- Edmunds, J.J., Hodges, J.C. "Medicinal chemistry of AT₂ receptors." In *Angiotensin Receptors*, Saavedra, J.M., Timmermans, P.B.M.W.M., Eds., pp. 119-134, Plenum Press, New York (1994).
- Gallinat, S. et al. "The angiotensin II type 2 receptor: An enigma with multiple variations." *Am. J. Physiol. Endocrinol. Metab.* **278**, E357-E374 (2000).
- Griendling, K.K. et al. "Angiotensin receptors and their therapeutic implications." *Annu. Rev. Toxicol.* **36**, 281-306 (1996).
- Timmermans, P.B.M.W.M. "Development of non-peptidic angiotensin II receptor antagonists." in: *Angiotensin II Receptor Antagonists*, Epstein, M., Brunner, H.R., Eds., pp. 89-103, Hanley & Belfus, Philadelphia (2000).
- Timmermans, P.B.M.W.M. et al. "Angiotensin II receptors and angiotensin II receptor antagonists." *Pharmacol. Rev.* **45**, 205-251 (1993).
- Wexler, R.R. et al. "Non-peptide angiotensin II receptor antagonists: The next generation in antihypertensive therapy." *J. Med. Chem.* **39**, 625-656 (1996).

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), on the basis of 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 biphenyl-tetrazole class of non-peptide antagonists, whereas the tetrahydroimidazolepyridines behave as selective non-peptide AT₂ receptor antagonists. The octapeptide saralasin, [Sar¹,Ala⁸]-Ang II, does not discriminate between AT₁ and AT₂ receptors. On the other hand, the peptide CGP42112A possesses high affinity for the AT₂ receptor and may act as a selective agonist.

The sequence identity between the AT₁ (359 aa) and AT₂ (363 aa) receptors is only 34%, but both receptors belong to the seven transmembrane domain receptor superfamily. In man, 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. The mouse AT_{1A} and AT_{1B} receptor genes are located on chromosomes 13 and 3, respectively. The AT₁ receptor is expressed in vascular smooth muscle, liver, kidney, heart, lung, adrenal cortex, pituitary and brain. Upon stimulation, the AT₁ receptor is coupled to G proteins and can activate several intracellular signaling mechanisms involving phospholipases C, D and A₂, adenylyl cyclase, MAP kinase and the Jak/STAT

pathway. Mouse, rat and human AT₂ receptor genes have been mapped to the X-chromosome and no subtypes or splice variants have been described. AT₂ receptors most likely activate tyrosine and serine/threonine phosphatases resulting in a decrease in MAP kinase activity, an opening of delayed-rectifier potassium channels and closing of T-type calcium channels. The AT₂ receptor is highly expressed in fetal tissues and is also found in adult adrenal medulla, brain and reproductive organs.

So-called atypical receptors for angiotensin peptides, exhibiting little or no affinity for non-peptide AT₁ and AT₂ receptor antagonists, have been identified in mammals as well as in non-mammalian vertebrates, including amphibians, birds and fish. However, their amino acid sequences and intracellular signaling pathways indicate that they are more closely related to the AT₁ receptor. High affinity binding sites selective for Ang IV and Ang (1-7), lacking affinity for non-peptide AT₁ and AT₂ receptor antagonists, have been demonstrated. Finally, a cytosolic Ang II binding protein and a nuclear Ang II binding site have been characterized.

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 and prevent cardiovascular hypertrophy and cardiac failure mediated by activation of the renin-angiotensin system. The functional correlate(s) of the AT₂ receptor remain(s) incompletely understood. Stimulation of AT₂ receptors may produce opposite effects to those mediated by AT₁ receptors.

Since AT₁ receptor blockade leads to elevated circulating Ang II concentrations, the participation of AT₂ receptor stimulation in the beneficial effects of AT₁ receptor antagonists is an attractive, but still hypothetical possibility.

Angiotensin Receptors

CURRENTLY ACCEPTED NAME	AT ₁ ^a	AT ₂
STRUCTURAL INFORMATION^b	359 aa (human)	363 aa (human)
RECEPTOR AGONISTS (PEPTIDE)	Ang II (A 9525) > Ang III (10385)	Ang II (A 9525) = Ang III (10385) CGP42112A (C-160)
RECEPTOR AGONISTS (NON-PEPTIDE)	L-162,313 L-163,491	—
RECEPTOR ANTAGONISTS (PEPTIDE)	Saralasin (A 2275)	Saralasin (A 2275)
RECEPTOR ANTAGONISTS (NON-PEPTIDE)	DuP 753 (Losartan) E3174 (active metabolite of Losartan) SKF-108566 (Eprosartan) TCV-116 (Candesartan) L-158,809 SR 47436 (Irbesartan) CGP48933 (Valsartan) BIBR277 (Telmisartan) CS-866 (Olmesartan)	PD 123,177 PD 123,319 (P-186) PD 126,055 EXP801 L-159,686 L-161,638
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG) G _i (cAMP modulation) Increase in MAP kinase Increase in Jak/STAT	Activate Tyr and Ser/Thr phosphatases Decrease in MAP kinase
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

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-diphenylcarbamoyl-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'-(butyloxycarbonyl)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-benzoyloxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid
SKF 108566: (αE)-α-[[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, turkey) have also been cloned.