

Angiotensin Fig. 1 2) 8) AT_{1a}, AT_{1b}, AT₃ AT₄ 가

Angiotensin II 수용체 아유형 Angiotensin 가
 Type 1(AT₁) Type 2(AT₂)가 1)5)9)10) AT₁ 수용체
 Angiotensin Angiotensin AT₁ Angiotensin 가 AT₁ G -
 Angiotensin protein Angiotensin

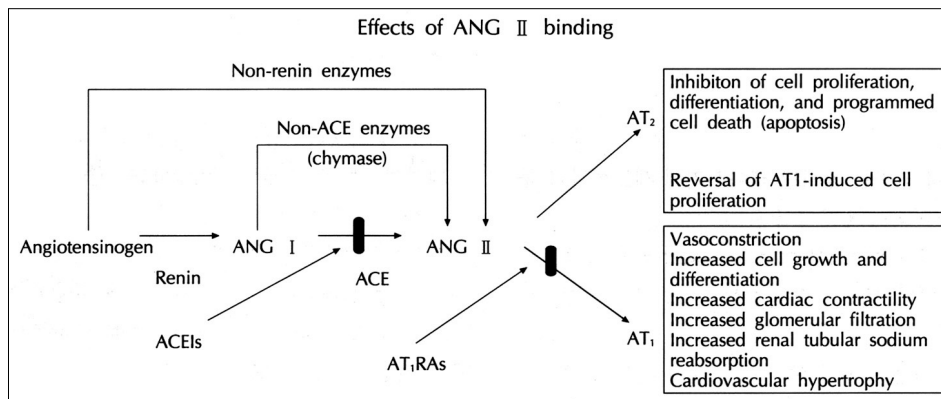


Fig. 1. Pathway of Angiotensin (ANG) generation, site of actions of Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin receptor antagonists (AT₁Rs), and effects of Angiotensin binding to Angiotensin type 1 (AT₁) and type 2 (AT₂) receptors. The effects of AT₁Rs on vascular tone and cell growth and differentiation may be the result of unopposed Angiotensin binding to the AT₂ receptor.

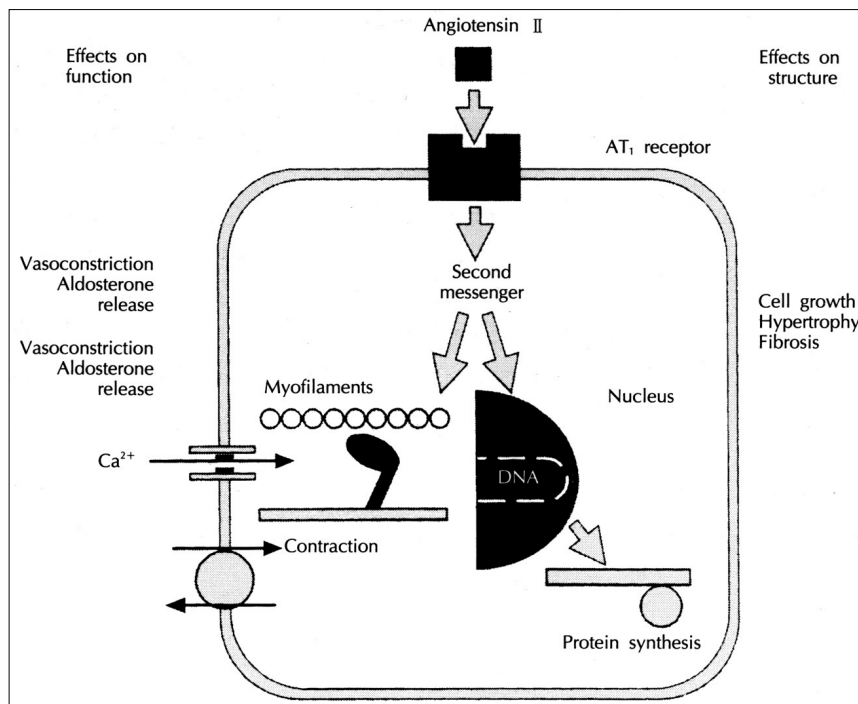


Fig. 2. Short- and long-term changes consequent on binding at the Angiotensin receptor.

3)11)

Angiotensin (slow response)

Angiotensin 가 AT₁ Fig. 2 AT₁ , , , ,

AT₂ 수용체 AT₁

AT₂ (fetal tissue)

AT₂ 가

AT₁

AT₁ (angio - nesis)

AT₂ AT₁ 가 Apoptosis (programmed cell death) 14 - 17)

RAS의 억제

RAS

ACE RAS 1 - 3)9)18)

Angiotensin AT₁ receptor antagonists (AT₁RAS)가 ACE 21)

AT₁RAS가 An - giotensin ACE ACE inactive decapeptide

Angiotensin active octapeptide Angiotensin

Angiotensin non - ACE 7) ACE

chymase

RAS

ACE (specific enzyme)가

bradykinin tachykinin

ACE bradykinin 가

dry, irritating cough

AT₁RAS bradykinin

AT₁ receptor AT₂

Renin feedback

plasma renin activity 가 Angiotensin 8)22)

AT₁RAS AT₁

Angiotensin AT₂

ACE repair 가

(Table 1).

Biphenyl tetrazoles Losartan, Candesartan, Irbesartan, Tasosartan

Non - biphenyl tetrazoles Eprosartan, Tel - misartan

Non - heterocyclic Valsartan

(Table 2).

untreated pigs²³⁾ Angiotensin

가 plasma 5 가

Angiotensin 75%

Captopril Angiotensin

Angiotensin

Angiotensin renin

가 Angiotensinogen

Angiotensinogen

cardiac Angiotensin

Table 1. Pharmacological effects of AT₁ receptor blockers and ACE inhibitors

	AT ₁ receptor blockers	ACE inhibitors
AT ₁ stimulation	↓ ↓	↓
AT ₂ stimulation	↑	↓
Plasma renin activity	↑	↑
Angiotensin levels	↑	↓
Bradykinin levels	=	↑

Table 2. Angiotensin receptor antagonists : comparative human pharmacokinetics

Compound (active metabolite)	Bioavailability (%)	Food effect	Active metabolite	Half-life (h)	Protein binding (%)	Dosing (mg)
Losartan (E3174)	33	Minimal	Yes	2 6 - 9	98.7 99.8	50 - 100 qd to bid
Candesartan (CV-11974)	40	No -	Prodrug	9	99.5	2 - 16 qd
Irbesartan	60 - 80	No	No	11 - 15	90.0	150 - 300 qd
Tasosartan (Enoltasosartan)	N/A	No	Yes	3 - 7 34 - 43	N/A	N/A
Valsartan	25	↓ 40 - 50%	No	6	95.0	80 - 320 qd

가 .

AT₁RAS

AT₂ 가 .

Angiotensin

. AT₁- catecholamine , ,

가 가

Angiotensin RAS AT₁

Angiotensin AT₂

가 가 3)24)

. /

. Angiotensin - mediated aldosterone

. AT₂

prostacyclin

. Angiotensin 10)25 - 27)

ACE AT₁RAS

thiazides, Kahan²⁸⁾ 115

β - , ACE

Thiazides dihydropyridine Irbesartan Atenolol

Irbesartan 가

Atenolol 8%

Angiotensin

ACE Angiotensin

가

Angiotensin 29)

가

35) ACE

(organ protection) bradykinin

REFERENCES

- 1) Unger T, Chung O, Csikos T, Culman J, Gallinat S, Gohlke P, et al. Angiotensin receptors. *J Hypertens* 1996; 14 (suppl):S95-S103.
- 2) Unger T, Culman J, Gohlke P. Angiotensin receptor blockade and end-organ protection: Pharmacological rationale and evidence. *J Hypertens* 16 (Suppl 7):S3-S9.
- 3) McInnes G. Angiotensin antagonists. Science Press Ltd;1998. p.1-47.
- 4) Daemen MJAP, Lombardi DM, Boaman FT, Schwartz SM. Angiotensin induces a smooth muscle cell proliferation in the normal and injured rat arterial wall. *Circ Res* 1991;68:450-6.
- 5) Falkenhahn M, Franke F, Bohle RM, Zhu YC, Stauss I-M, Bachmann S, et al. Cellular distribution of Angiotensin converting enzyme after myocardial infarction. *Hypertension* 1995;25:219-25.
- 6) Unger T, Gohlke P, Paul M, Rettig R. Tissue renin-Angiotensin systems: Fact or fiction? *J Cardiovasc Pharmacol* 1991;18 (suppl 2):S20-S25.
- 7) Husain A. The chymase-Angiotensin system in humans: Editorial review. *J Hypertens* 1993;11:1155-9.
- 8) Wolny A, Clozel J-P, Rein J, Mory P, Vogt P, Turino M, et al. Functional and biochemical analysis of Angiotensin-forming pathways in the human heart. *Circ Res* 1997; 80:219-27.
- 9) Bauer JH, Reams GP. The Angiotensin type receptor antagonists: A new class of antihypertensive drugs. *Arch Intern Med* 1995;155:1361-8.
- 10) Booz EW, Baker KM. Role of type 1 and type 2 Angiotensin receptors in Angiotensin-induced cardiomyocyte hypertrophy. *Hypertension* 1996;28:635-40.
- 11) Dzau VJ, Mukoyama M, Pratt RE. Molecular biology and Angiotensin receptors: Target for drug research? *J Hypertens* 1994;12:S1-S5.
- 12) De Gasparo M, Husain A, Alexander W, et al. Proposed update of Angiotensin receptor nomenclature. *Hypertension* 1995;25:924-7.
- 13) Haywood GA, Gullestad L, Katsuya T, et al. AT₁ and AT₂ Angiotensin receptor gene expression in human heart failure. *Circulation* 1997;95:1201-6.
- 14) Stoll M, Steckelings UM, Bottari SP, Unger T. Regulation of endothelial cell growth: Role of the Angiotensin AT₂-receptor [abstract]. *Circulation* 1993;88(suppl):469.
- 15) Zhu YZ, Zhu YC, Chung O, Spitznagel H, Sandmann S, Unger J. Increased gene expression of Angiotensin AT₁ and AT₂ receptors in the acute phase of myocardial infarction [abstract]. *Hypertension* 1996;26:694.
- 16) Stoll M, Steckelings UM, Paul M, Bottari SP, Metzger R, Unger T. The Angiotensin AT₂ receptor mediates inhibition of cell proliferation in coronary endothelial cells. *J Clin Invest* 1995;95:651-657.
- 17) Ford WR, Clanachan AS, Jugdutt BI. Opposite effects of Angiotensin AT₁ and AT₂ receptor antagonists on recovery of mechanical function after ischemia-reperfusion in isolated working rat hearts. *Circulation* 1996;94:3087-98.
- 18) Csajka C, Buclin T, Brunner HR, Biollaz J. Pharmacokinetic-pharmacodynamic profile of Angiotensin receptor antagonists. *Clin Pharmacokinet* 1997;32:1-29.
- 19) Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996;334:1649-54.
- 20) Messerli FH, Weber MA, Brunner HR. Angiotensin receptor inhibition: A new therapeutic principle. *Arch Intern Med* 1996;156:1957-65.
- 21) Gohlke P, Linz W, Schölkens BA, Wiemer G, Unger T. Cardiac and vascular effects of long-term losartan treatment in stroke-prone spontaneously hypertensive rats. *Hypertension* 1996;31:397-402.
- 22) Richer-Giudicelli C, Fornes P, Cazaubon C, Nisato D, Giudicelli J-F. Effects of Angiotensin AT₁ receptor blockade on survival, systemic and coronary hemodynamics and cardiac remodeling in postischemic heart failure in rats. *Circulation* 1997;96(suppl):3605.
- 23) van Kats JP, Danser AHJ, van Meegen JR, Sassen LMA, Verdouw PD, Schalekamp MADH. Angiotensin production in the heart. A quantitative study in pigs with the use of radiolabeled Angiotensin infusions. *Circulation* 1998;98:73-81.
- 24) Man in't Veld AJ. Clinical overview of irbesartan: Expanding the therapeutic window in hypertension. *J Hypertens* 1997;15 (suppl 7):S27-S33.
- 25) Dahlf B. The importance of the renin-Angiotensin system in the reversal of left ventricular hypertrophy. *J Hypertens* 1993;11 (suppl 3):S29-S35.
- 26) Dahlf B. Effect of Angiotensin blockade on cardiac hypertrophy and remodelling: A review. *J Hum Hypertens* 1995;9(suppl):S37-S44.
- 27) Dahlf B, Penneri K, Hansson L. Reversal of left ventricular hypertrophy in Hypertensive Patients: A Metaanalysis of 109 Treatment Studies. *Am J Hypertens* 1992;5:95-110.
- 28) Kahan T, Malmqvist K, Edner M, Held C, Osbakken M. Rate and extent of left ventricular hypertrophy regression: A comparison of Angiotensin blockade with irbesartan and beta-blockade [abstract]. *J Am Coll Cardiol* 1998; 31:212A.
- 29) Kahan T. The importance of left ventricular hypertrophy in human hypertension. *J Hypertens* 1998;12 (suppl 7): S23-S29.
- 30) Capers Q IVth, Laursen JB, Fukui T, Rajagopalan S, Mori I, Lou P, et al. Vascular thrombin receptor regulation in hypertensive rats. *Circ Res* 1997;80:838-44.
- 31) Chobanian AV. Comparison of the effects of ACE inhibition and AT₁ receptor blockade on atherosclerosis [abstract]. *Am J Hypertens* 1998;11:238A.
- 32) Asano K, Dutcher DL, Port JD, et al. Selective downregulation of the Angiotensin AT₁-receptor subtype in failing human ventricular myocardium. *Circulation* 1997; 95:1193-200.
- 33) Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study). *Lancet* 1997;349:747-52.
- 34) Vijay N, Alhaddad LA, Marty Denny D, Ruff D, Yasin M, Yellen L, et al. Irbesartan compared with lisinopril in patients with mild to moderate heart failure. *J Am Coll Cardiol* 1998;31:68A.
- 35) Zierhut W, Studer R, Laurent D, et al. Left ventricular wall stress and sarcoplasmic reticulum Ca²⁺-ATPase gene expression in renal hypertensive rats: Dose-dependent effects of ACE inhibition and AT₁-receptor blockade. *Cardiovasc Res* 1996;31:758-68.