REVIEW ARTICLE

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Angiotensin Receptor Antagonists a New Class of Antihypertensive Drugs

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Losartan is an orally active, non-peptide Angiotensin II (AT_1specific) antagonist. It is a new and promising antihypertesive agent, better than ACE inhibitors in controlling hypertesion. Its antihypertensive effect is enhanced when given in combination with hydrochlorthiazide (HCT) or an ACE inhibitor. Among other angiotensin receptor antagonists are TCV- 116, CV-11974, and CV-11194, all of which seem to be promising antihypertensives of the future. Results of the studies on losartan and other angiotensin receptor antagonists indicate that they would certainly acquire a commanding position in the treatment of hypertension, a disease that makes millions of people suffer.

AN active drug discovery process has produced a new class of pharmacological agents for the treatment of hypertension every ten years, from diuretics in the 1960 to beta adrenoceptor blockers in 1970 followed by calcium channel blockers and Angiotension converting enzyme (ACE) inhibitors in the 1980. All these agents have had beneficial effects in the disease but also have some limitations. An extension to the ACE inhibitors in hypertension, the Angiotensin receptor antagonists appear to be the drugs of future for the current decade. The present article describes the concept and pharmacology of this novel class of antihypertensive drugs.

Significance of the renin-angiotensin-aldosteron system (RAS) in hypertension:

The involvement of the RAS particularly Angiotension II (Ang II), in the pathogenesis of hypertension **(Fig. 1)** is widely acknowledged and is supported by various observations which are as follows:

1) The RAS has been shown to be critically involved in the development of experimental hypertension[1] and the activation of the RAS system appears to be the crucial factor involved in producing a rise in BP.[2]

2) ACE inhibitors are particularly efficacious when the raised BP results from an excess renin production (renovascular hypertension)[3].

3) Drugs, such as ACE inhibitors, which interfere with the production of Ang II reduce BP in a large number of hypertensive patients[4] and after ACE inhibition Ang II virtually disappears from the circulation.[5]

It is also now clear that the chronic BP elevation caused by circulating (and perhaps locally produced) Ang II may have adverse effects on organ function. Ang II plays a significant role in the development of left ventricular hypertrophy in hypertension.[6] In addition, cardiac RAS may contributeto the pathophysiology of heart ailure.[6] Experimental and clinical studies with ACE inhibitors point to a role for tissue ACE activity in the development of atherosclerosis, as well as cardiac hypertrophy and remodeling. Ang II can induce vascular hypertrophy and facilitation of sympathetic activity on vascular targets.[7]

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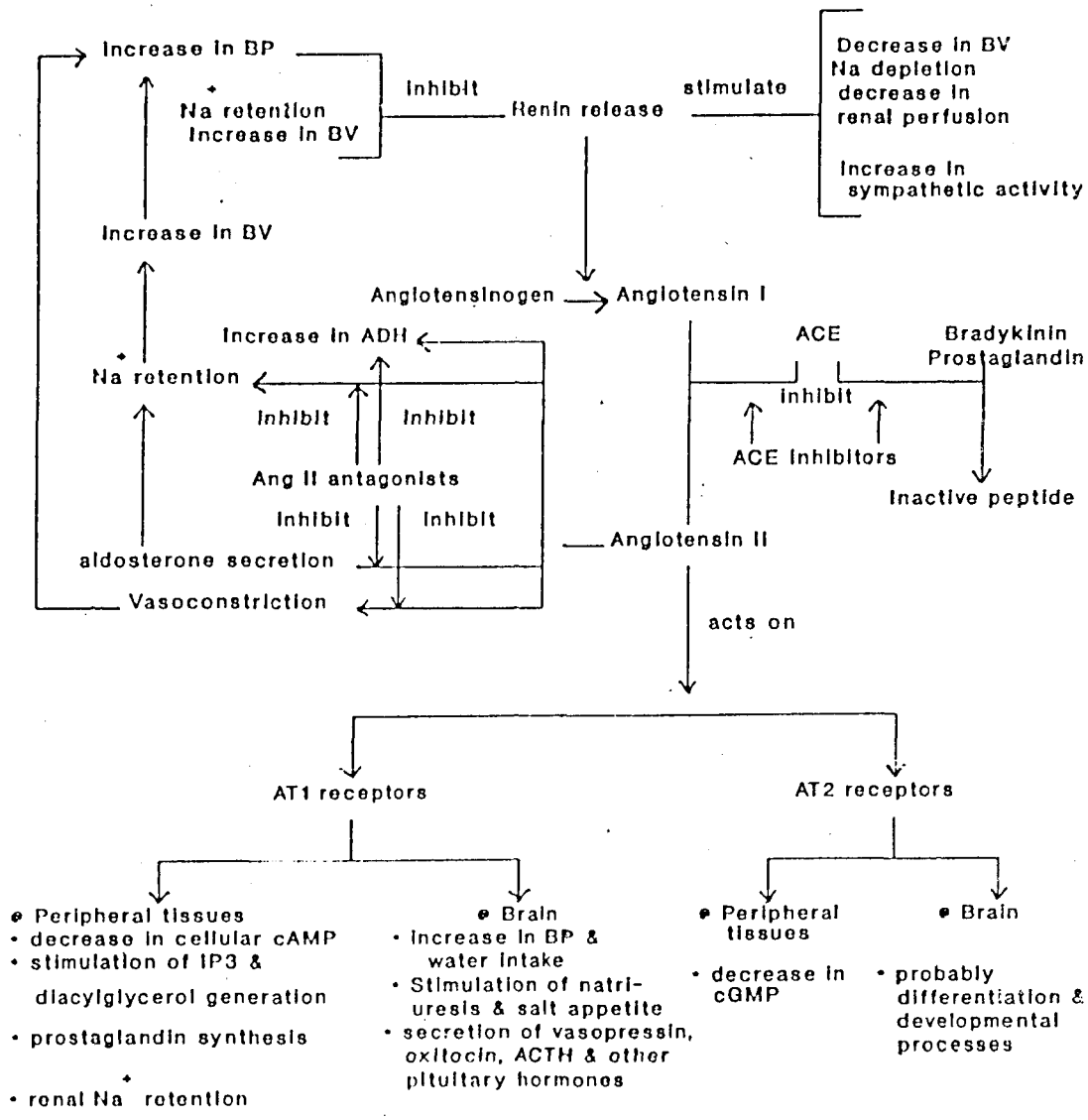
FIG.1 SCHEMATIC REPRESENTATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM



BP-blood pressure

BV-blood volume

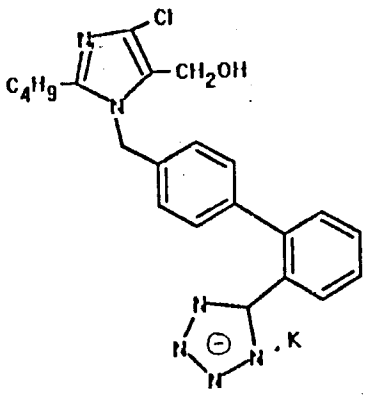
ADH-antidiuretic hormone

ACTH-adrenocorticotropic hormone

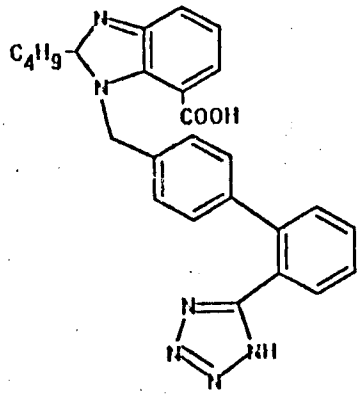
Ang II receptors

Indirect evidence has accumulated over the years for the existence of different subtypes of Ang II receptors.[8] Pharmacological evidence for two specific receptor subtypes has only recently been found following the development of highly selective Ang II receptor ligands such as losartan (Dup 753),

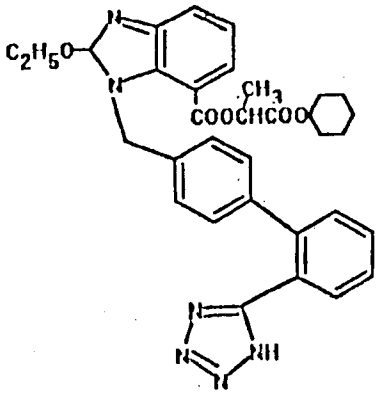
Fig. 2 : Structural formulae of a few angiotensin receptor antagonists



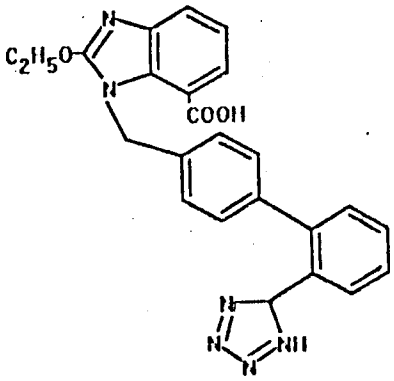
Dup 753 (Losartan)



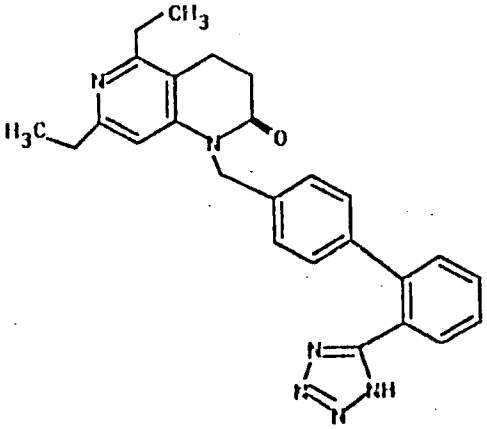
CV - 11194



TCV - 116



CV 11974



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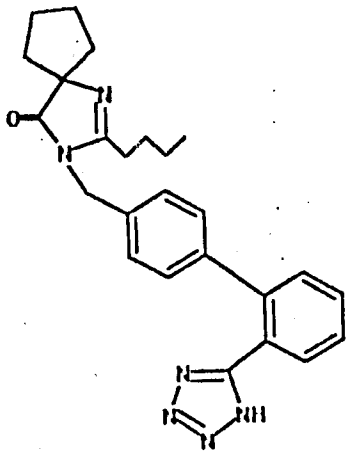

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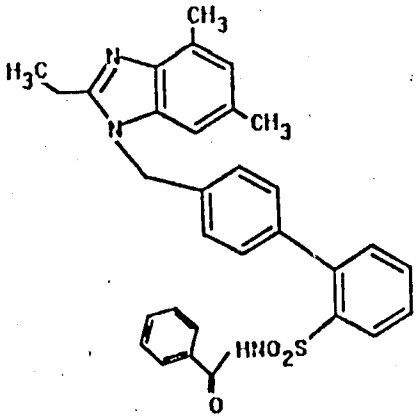

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CGP42112A and PD123177[9-11]. Receptors with highest affinity for losartan and lowest affinity for CGP42112Aand PD123177 are referred to as AT_1 receptors. Conversely, receptors showing highest affinity for CGP42112A and PD123177 and lowest affinity for losartan are referred to as AT_2 receptors.[12] Sulfhydryl reducing agents such as dithiothreitol and glutathione are also able to distinguish the two receptor subtypes. These two compounds inhibit the binding of Ang II to AT_1 receptors, whereas they enhance the binding affinity of Ang II for AT_2 sites.[9,13] Recently the existence of two structurally distinct AT_1 receptor isoforms (AT_{1a} and AT_{1b}) has also been reported.[14]

Ang II receptors in brain: A number of reports have been published describing the distribution of Ang II receptor subtypes in brain using either quantitative autoradiography or competitive radioligand binding techniques.[15-20] The distribution of AT_1 and AT_2 receptors within the brain was almost identical in all studies and is reported to differ with age and species.[15-20]. AT_1 receptors were localised mainly in target sites involved in regulation of BP, drinking, salt, appetite and vasopressin formation and release [18,19], whereas the distribition of AT_2 receptors in adult rats did not provide definitive clues to their functions.[20]

Ang II receptors in peripheral tissues: In peripheral tissues, AT_1 and AT_2 receptors seem to mediate the biological actions of Ang II through different signal transduction pathways. AT_1 receptors interact with proteins, inhibiting adenylyl cyclase activity and stimulating phospholipases C, A_2 and D. This in turn causes a decrease in cellular cAMP, and a stimulation of both inositol 1,4,5-triphosphate (IP_3) and diaclyglycerol generation as well as prostaglndin synthesis.[21-23] In contrast, AT_2 receptors do not interact with G proteins.[24] Summers et al.[25] and Bottari et al.[26] have recently shown that stimulation of AT_2 receptors lead to a decrease of cGMP levels. This decrease is probably caused by an inhibition of particulate guanylyl cyclase following the stimulation of a phosphotyrosine phosphatase.[26]

Effects of central and peripheral Ang II receptors stimulation: Stimulation of Ang II receptors in brain evokes responses that include an increase in BP and water intake, stimulation of natriuresis and salt appetite, secretion of vasopressin, oxytocinm adreno-corticotropic hormone and other pituitary hormones, and an interaction with brain catecholamines.[27] Peripheral Ang II receptors mediate the same effects on cardiovascular and fluid regulation. However, unlike central Ang II receptors, peripheral Ang II receptors mediate the renal Na+retention.[28]

How effective are ACE inhibitors in hypertension?

ACE inhibitors are used widely in the treatment of hypertension and congestive cardiac failure.[29-32] The major biochemical site of action of ACE inhibitors is known to be plasma and tissue ACE. However since Ang II is detected readily in plasma and tissues despite ACE inhibition[33d] we are left wondering if ACE is preeminent for Ang II formation in vivo. Moreover, different ACE-inhibitors inhibit the enzyme in different tissues to varying degrees. An ideal ACE inhibitor should be able to inhibit the enzyme to a high degree not only in plasma but also in other tissues. Although many studies are being carried out and the never ACE inhibitors are being scrutinised more exhaustively, no such pharmacological agent has been discovered yet.

Angiotensin II receptor antagonists

Losartan, TCV116, CV11194, CV11974, BIBR-2127, Valsartan, ZD- 7155, ICI-D-8731, YM-358, RWJ-38970, FK-739, L-159282 and CI-996 are various Ang II receptor antagonists that are being studied for their clinical efficacy in various forms of hypertension. Others like SC-52428, WAY-126227, FR-130739, WK-1260, KT3-671, GA-0056, A-81282, L-158809, GR-138950, U-97018, BMS-180560, CGF- 48933 and PD-150304 are being evaluated

Table 1: Angiotensin-II receptor antagonist currently under development*

No.	Compound	Company of Origin	Current status of Development	Remarks
1.	BIBR-277	Dr. Karl Thomae	Clinical Phase-I	—
2.	SC-52428	Searle	Pre-clinical	Devoid of agonistic Property
	SC-51895		Pre-clinical	Effective in the treatment
	SC-50560		Pre-clinical	of HT & CHF
3.	WAY-126227	Wyeth-Ayerst	Pre-clinical	In-vivo equivalent to losartan & captopril
4.	YM-358	Yamanouchi	Clinical	Long-acting
	YM-31473		Pre-clinical	Pro-drug, longer duration of action
5.	RWJ-38970	R.W. Johnson	Clinical	1-3 and 1.5-biphenyl-substituted-3-mercapto-triazole
	RWJ-46458		Pre-clinical	Superior to losartan, not induced reflex Tachycardia
6.	FR-130739	Fijisawa	Pre-clinical	—
	FK-739		Clinical Phase-II	—
7.	WK-1260	Wakunaga	Pre-clinical	—
	WK-1492		Pre-clinical	—
8.	L-61816	Merck & Co.	Pre-clinical	—
	L-162154		Pre-clinical	Heterocyclic and related arylsulphonamide effect last for more than 5 hrs.
	L-162234		pre-clinical	Potent oral & i.v.
	L-161177			Imidazopyridine base phenoxyphenyl acetic acid replacing the biphenyl tetrazole
	L-158659		pre-clinical	Short acting
	L-159282		Clinical	Benzoyl sulphonamide group
9.	KT3-671	Kotobuki-Seiyaku	Pre-clinical	No-intrinsic agonistic activity. Pyridine derivative
10.	ICI-D-8731	ICI Pharmaceuticals	Clinical Phase-II	Long-acting
11.	GA-0056	Green Cross & Asahi Glass	Pre-clinical	Long-acting, quinolone derivative
12.	A-81282	Abbott	Pre-clinical	Good safety profile
	A-81988		Pre-clinical	Long-acting & 30 times more potent than losartan
13.	L-158809	Merck, Sharp & Dohme	Pre-clinical	Efficacy equal to ACE inhibitors
14.	CI-996	Warner-Lambert	Clinical Phase-II	—
15.	GR-138950	Glaxo	Pre-clinical	High oral bioavailability
	GR-117289		Pre-clinical	Benzofuran derivative
16.	U-97018	Upjohn	Pre-clinical	—
17.	BMS-180560	Bristol, Mayer & Squibb	Pre-clinical	—
18.	CGF-48933	Ciba-Geigy	Pre-clinical	Potent than losartan
19.	PD-150304	Parke-Devis	Pre-clinical	1-benzylimidazole-5-methyliedene hydantoin
20.	SR-47436	Elf-Sanofi	Clinical Phase-II	—

*compiled from DRUG NEWS & PERSEPCTIVE Vol. 5,6,& 7; 1992-1994.

pre-clinically in different animal models. The list of selective AT_1 receptor antagonists under devlopment either in clinically or phases in the pre-clinically state are shown in Table 1. Currently, selective antagonists of AT_1 receptor such as losartan and of AT_2 receptor such as PD 123319 are available, but there are no selective antagonists that differentiate between AT_{1a} and AT_{1b}. As the AT_1 mediates most of the known actions of Ang II, and AT_1 antagonist should provide an effective blockade of the RAS system and may result in a more complete inhibition than that produced by ACE inhibitors. However, ACE inhibition may exert addtional BP lowering action via increased bradykinin levels and the endothelium-derived relaxing factor.[34,35]

Chemistry of Angiotensin receptor antagonists

DuP 753 (losartan), CV-11194, CV-11974, and TCV-116 are benzimidazole carboxylic acid derivatives. A series of 2- substituted-1-[biphenl-4-yl) methyl]-1H-benzimidazole-7- carboxylic acids were prepared from the key intermediate 3-amino- 2 [[(biphenul-4-yl)methyl] amino] benzoate in order to clarify the structures activity relationships (SAR) of various analogues. The SAR studies on the binding affinity and the inhibition of Ang II induced pressor response suggested that straight chains of a certain length (ethoxy or ethyl) are the best as substituents at the 2-position and that their stearic factors, lipophilicity, and electrophilic effects affected the potency of the Ang II antagonistic action. Both a carboxyl group at the 7-position and a tetrazole ring at the 2-position are particularly important for a potent oral a Ang II antagonistic activity and a long-acting hypotensive effect.[36]

Losartan: A novel antihypertensive

Losartan potassium is a member of a new class of drugs, which act by specific blockade of the actions of Ang II. It is the first Ang II receptor antagonist to be developed for clinical use, and offers potential therapeutic benefits. Losartan has been proved to be useful in the treatment of hypertension and chronic heart failure as it exhibits high affinity and specificity for AT_1 receptors. In addition, its active metabolite, E-3174, exhibits even greater affinity for the AT_1 receptor and has a longer duration of action than the parent compound. E-3174 is responsible for the long-lasting activity of losartan in controlling BP.[37]

Losartan and the renin-angiotensin system (RAS):

In normal volunteers, losartan (25-100 mg) causes a dose-related- inhibition of exogenous Ang II pressor repsonses and this is accompanied by characteristic changes in the circulating components of the RAS. Plasma renin activity is increased in a dose-related manner, and so is the plasma Ang II. The angiotensin I (Ang I) levels are not changed much and there is a reduction in plasma aldosterone, particularly in long-term studies.[38]

Alteration of the RAS by diet (salt depletion or repletion) or diuretics profoundly modifies the haemodynamic effects of losartan. In salt replete normotensives, losartan (upto 100 mg) has little effect on BP or heart rate. Sodium depletion leads to a dose-related fall in supine and standing systolic and diastolic BP after 25-100 mg losartan. Activation of the RAS by diet (salt depletion or repletion) or diuretics enhances the neuroendocrine and haemodynamic effects of losartan.[38]

Effectiveness of losartan in clinical treatment of hypertension Clinical aspects

Losartan is the first orally active non-peptide Ang II receptor (AT_1 specific) antagonist to demonstrate antihypertensive efficacy in large scale clinical hypertension trails.[39-40] The antihypertensive effect of losartan (50-100 ng) administered once daily was equivalent to felodipine (extended release, 5-10 mg) in older hypertensives (>65 years) after 12 weeks of therapy. Similarly the administration of losartan (50-100 mg) once daily produced a significantly greater antihypertensive effect than captopril (50-100 mg) given once daily. The antihypertensive effect of

losartan (50 mg) administered once daily was demonstrated to be similar to enalapril (20 mg) administered daily.[39]

Safety profile: The safety of losartan has been assessed in double-blind controlled clinical trials conducted in over 2500 patients with incomplicated mild, moderate and severe essential hypertension. Overall both losartan and losartan plus HCT were well tolerated in these clinical trials. The adverse effects profile of losartan was similar to placebo. The drug-related clinical adverse effects include dizziness, oedema, hyperkalemia (comparable to ACE inhibitors), cough (incidence was less than ACE inhibitors), increased alamine aminotransferse. The overall rate of patient discontinutation due to clinical adverse experiences on losartan and losartan plus HCT therapy was 2.3% and 2.8% respectively, compared to placebo (3.7%).[40]

Losartan and ACE inhibitors

Losartan induces changes in BP, renal haemodynamics, proteinurea, and serum lipids that are similar to those induced by ACE inhibitors. Like ACE inhibitors losartan too is clinically effective in treating hypertension in patients with renal disease and has a renal 'protective' profile, Recent pharmacokinetic data on losartan and its active metabolite in patients with several degrees of renal function loss suggest that no dosage adjustment is needed in the presence of renal insufficiency.[41]

ACE inhibitors produce renal vasodilation, a reduction of proteinurea and an increase of specific serum lipids. These effects may be probably due to bradykinin accumulation. The beneficial effects of ACE inhibitors on BP, renal haemodynamic function, proteinurea and serum lipid profile were comprable with those obtained during treatment with losartan (50-100 mg daily) for a four week period.[41]

In the phase IIb, dose range finding study (25-100 mg q.d) in Japan, the percentage of responders to losartan was 71% (95/135) which is similar to that of ACE inhibitors. In the same study, drug-induced cough was not observed. This is probably so because losartan lacks ACE (Kininase II) inhibitory activity and hence does not affect bradykinin receptors; the dry cough, which is a typical adverse effect of ACE inhibitors is thought to be caused by bradykinin accumulation.[37]

Antihypertensive efficacy in combination with Hydrochlorothiazide (HCT)

Losartan in once-daily doses provides 24-hour antihypertensive efficacy. The effect of losartan (50 mg/day) can be enhanced by combination with low dose diuretic HCT (12.5 mg daily). During losartan treatment there was neither any change in heart rate or body weight, nor were there any symptomatic side effects. Losartan counteracts the unwanted effects of diuretic treatment on plasma potassium, uric acid and glucose levels.[42]

Uricosuric effect of Losartan

An uricosuric effect of losartan has been observed in the laboratory findings of the clinical studies. Since high serum uric acid level is one of the risk factors for coronary heart disease, losartan may offer a distinct advantage over other antihypertensive drugs.[37]

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ERRATUM

The sentences on page 38 in January-February 1995 issue "In this context, ... three at 150 rpm" to read as given below:

"In this context, a close scrutiny of the results reveals that for product A there was one incidence of tablet failure at 100 rpm. For product B there was one tablet failure at 50 rpm and 100 rpm each and two at 150 rpm".