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Scientific Update™

The role of AT_1 receptors in target organ disease: A functional perspective

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Angiotensin-II antagonists are the newest form of medication for the treatment of hypertension. Inhibition of the renin-angiotensin system, which contributes to the pathogenesis of hypertension and heart failure, may be more complete with AII antagonists as compared to other antihypertensive drugs. As a class, they have favourable pharmacokinetics, antihypertensive action, and side-effect profiles. Candesartan, one of the newest A-II antagonists, is now available in Canada.

AT receptors in the heart and vasculature

The renin-angiotensin system (RAS) is a major contributor to blood-pressure homeostasis. Its effector is angiotensin-II (A-II), an octapeptide hormone that controls electrolyte balance, blood volume, and arterial blood pressure. Enzymatic components of the RAS represent the major systemic metabolic pathway leading to A-II synthesis, but other enzymes may produce A-II in tissues (Figure 1).

Within the RAS, angiotensin converting enzyme (ACE) inhibition clearly blocks A-II formation. However, several non-renin and non-ACE enzymes can ultimately convert angiotensinogen, then angiotensin-I into A-II.

A-II influences blood-pressure levels by activating receptors in many tissue and organ systems. Two main subtypes of cellular A-II receptors are AT_1 and AT_2. Most physiologic functions of A-II are mediated through AT_1 receptors. Their activation of smooth muscle cells leads to vasoconstriction, while their stimulation in cells of proximal renal tubules leads to higher sodium levels and water reabsorption (Figure 1).

A-II stimulates the thirst reflex and heightens activity of the sympathetic nervous system (SNS). It stimulates the release of:

- catecholamines from the adrenal medulla;
- aldosterone from the adrenal cortex; and
- vasopressin from the posterior lobe of the pituitary.

These AT_1 receptor-mediated actions increase peripheral resistance and blood volume, raising blood pressure. The hemodynamic changes lead to a greater cardiac workload and may cause cardiovascular hypertrophy and remodeling.

AT_1-receptor stimulation of vascular smooth muscle cells and cardiac myocytes leads to proliferation, hypertrophy, and hyperplasia. The generation of superoxide anions causes a form of oxidative stress that may lead to endothelial dysfunction or exacerbate atherosclerosis. This stress may activate transcriptional factors that power pro-inflammatory genes. Leukocyte activation and cellular infiltration follow; these processes contribute to foam-cell formation in atherosclerotic plaque and, potentially, to plaque rupture.

Through AT_1 receptors, A-II appears to affect plasminogen activator inhibitor (PAI)-1, which inhibits endogenous tissue plasminogen activator (tPA). This effect may perturb the balance of the blood-clotting system. Finally, A-II may directly affect platelets, leading to platelet activation and aggregation and contributing to the clinical events of myocardial or cerebral ischemia.

Recently, investigators have gained some insights into the function of AT_2 receptors. They appear to exert an antiproliferative effect, counteracting the growth stimulation mediated by AT_1 receptors.

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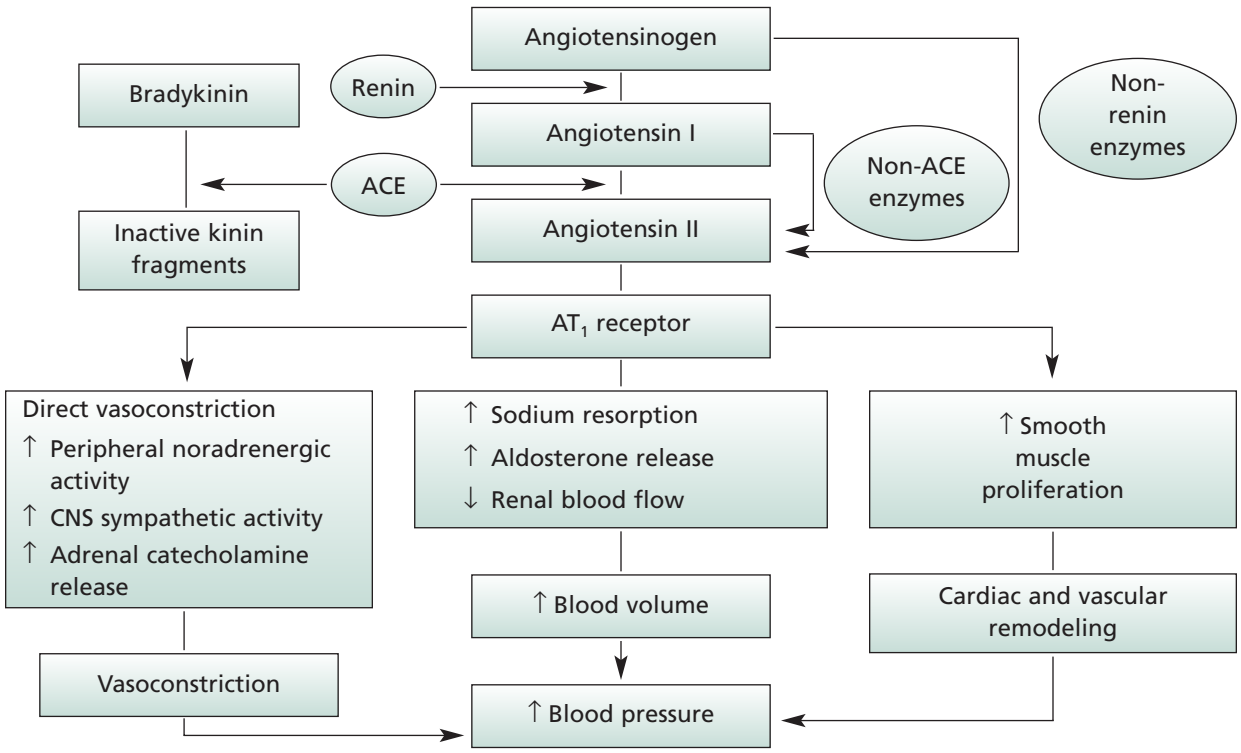
Figure 1: Role of the renin-angiotensin system in the pathogenesis of hypertension.



A-II antagonists block the AT_1-mediated actions of A-II, regardless of the route of A-II synthesis. Higher levels of circulating A-II may stimulate AT_2 receptors. In contrast, ACE inhibitors reduce the amount of synthesized A-II, reducing the activation of both AT_1 and AT_2 receptors.

Localization and function of AT_1 receptors

The distribution of AT_1 receptors has been mapped by in-vitro autoradiography in most tissues of many mammals, including humans. Not surprisingly, AT_1 receptors occur in sites that are targets for the physiologic actions of angiotensin, including:

- the adrenal cortex and medulla;
- renal glomeruli and proximal tubules;
- vascular and cardiac muscle;
- brain circumventricular organs.

A modestly high density of AT_1 receptors is found in the A-V node of the heart's conducting system. Their clinical significance remains uncertain.

AT_1 receptors: Coronary flow and flow reserve

The cardiac effects of hypertensive disease are multidimensional and include left ventricular hypertrophy (LVH), impaired coronary vascular hemodynamics, endothelial dysfunction, and fibrosis of the ventricular wall. Complications include cardiac arrhythmias, acceleration of epicardial coronary artery disease from atherosclerosis, ischemia, and left ventricular failure.

AT_1-receptor stimulation exacerbates abnormal systemic hemodynamic changes by further increasing arterial pressure and total peripheral resistance; hence, afterload is imposed upon the left ventricle. Detrimental changes in vascular hemodynamics within the heart progress due to increases in coronary vascular resistance and blood viscosity and reductions in coronary blood flow and flow reserve.

Experimental evidence has shown that combined use of an ACE inhibitor and an AT_1 receptor blocker reduces LV mass and improves intracoronary hemodynamics by increasing coronary blood flow and flow reserve and reducing coronary vascular resistance.

Renal responses to AT_1 receptor blockade

The intrarenal RAS is a critical paracrine regulator of renal hemodynamics and tubular transport function. Intrarenal A-II is made locally from systemically delivered and intrinsically formed angiotensin-I. Although A-II is dis-

Table 1: Pharmacologic characteristics of the angiotensin II receptor antagonists

	Losartan Potassium	Valsartan	Irbesartan	Candesartan Cilexetil
Active metabolite	(EXP3174)	No	No	Candesartan
AT_1 receptor[6] antagonism	Surmountable (EXP3174)-intermediate	Not studied	Intermediate	Insurmountable
Bioavailability	33%	23%	60-80%	15%
Absorption affected by food	Yes	Yes	No	No
% Protein binding	98-99%	95%	90%	99%
Routes of elimination	70% biliary, 30% renal	80% biliary	75% biliary	60% renal
Half-life (hr)	1.5-2.5 (losartan)	6	11-15	9
Proprietary name	Cozaar	Diovan	Avapro	Atacand
Dosing	50-100 mg	80-160 mg	150-300 mg	8-16 mg

Adapted from Ruddy and Kostis. Angiotensin II receptor antagonists. In: Oparil S, Weber M, eds. *Hypertension* 1999. In press.

tributed throughout the kidney, concentrations are not uniform. Medullary content per gram of tissue is four to five times higher than cortical content. In addition, compartmentalization of cortical A-II occurs in tubular fluid. High concentrations of A-II, A-I, and angiotensinogen in proximal tubules indicate that these cells secrete A-II or its precursors into tubular fluid. This activates A-II receptors on proximal and distal nephron segments.

In micropuncture studies, the activation of intraluminal AT_1 receptors has influenced sodium and bicarbonate transport by proximal and distal tubules and helped to regulate tubular reabsorption rate.

Recent studies have evaluated the effects of AT_1-receptor blockade with candesartan in a hypertensive rat model. When administered systemically, candesartan elicits marked decreases in systemic arterial pressure and has direct renal actions, e.g., increased glomerular filtration rate, renal blood flow, and absolute and fractional sodium excretion. The profound influence of candesartan in reducing the fractional sodium reabsorption rate and augmenting renal hemodynamics contributes to a sustained antihypertensive effect.

Pharmacology of AT_1 receptor blockers

A number of orally active, AT_1 receptor blockers are commercially available, e.g., losartan, valsartan, and irbesartan. Candesartan has recently been introduced in Canada. Others, e.g., eprosartan and tasosartan, are in development. These antihypertensive agents have proven efficacy and are being tested for use in other cardiovascular conditions.

AT_1-receptor blockers share a common mechanism of action but differ in structure and pharmacokinetic properties (Table 1). Specifically, they differ in oral bioavailability, absorption rate, tissue distribution, AT_1-receptor binding kinetics, metabolism, and elimination rate. AT_1 receptor binding profiles are illustrated in Figure 2. The insurmountable antagonism at the receptor level displayed by candesartan reflects tighter binding to and slow dissociation from the AT_1 receptor. This characteristic should lead to prolonged pharmacological and antihypertensive actions of the drug.

Unlike ACE inhibitors, the AT_1-receptor blockers do not interfere with enzymatic processes within the RAS. ACE inhibitors inactivate bradykinin. In contrast, AT_1-receptor blockers do not potentiate bradykinin, which is thought to contribute to the development of cough and angioedema associated with ACE-inhibitor use.

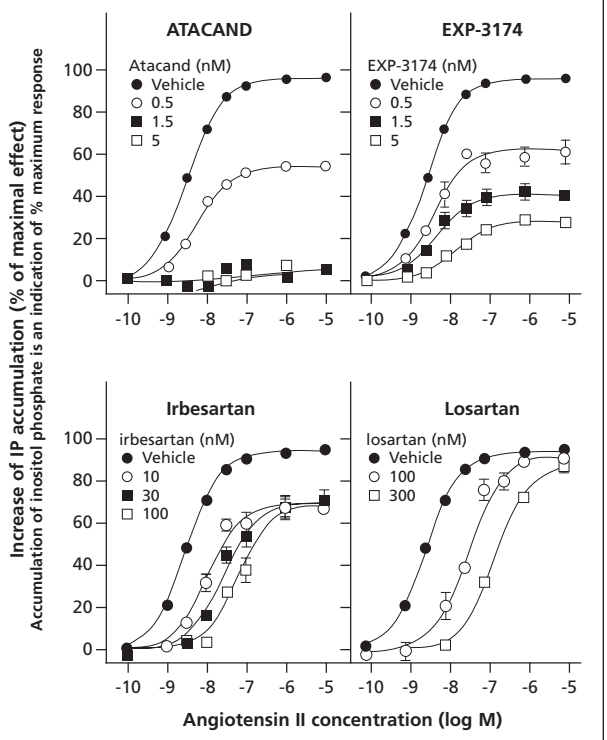
Comparisons of AT_1-receptor blockers

Several short-term studies that compare the relative antihypertensive efficacy of AT_1-receptor blockers have found small, but sometimes statistically significant, differences. In a double-blind study of 1,369 patients with mild-to-moderate hypertension, no significant difference was found between valsartan (80-160 mg) and losartan (50-100 mg) in lowering systolic and diastolic pressures after four and eight weeks of therapy. Both agents were superior to placebo.[1]

In a 567-patient study of mild-to-moderate hypertensives, both irbesartan (150 mg) and losartan (100 mg) significantly lowered systolic and diastolic pressure as compared to baseline and placebo at eight weeks. A higher dose of irbesartan (300 mg) significantly reduced systolic and diastolic pressure by an additional 25% (-3.0 mm Hg and -5.1 mm Hg, respectively) as compared to losartan (100 mg) ($p<0.01$ for both comparisons).[2]

Oparil et al, on behalf of the Irbesartan/Losartan Study Investigators[3] conducted a multi-centre, randomized,

Figure 2: Binding profiles of AT_1 receptor blockers[6]



double-masked, elective-titration study to compare the effectiveness, safety, and tolerability of irbesartan and losartan (two AT_1 receptor blockers) in the treatment of patients with mild-to-moderate hypertension. The mean change in trough mean seated diastolic blood pressure at week eight (the primary endpoint) was significantly greater in patients receiving irbesartan monotherapy (150-300 mg daily) than in those receiving losartan monotherapy (50-100 mg daily); (-10.2 mm Hg vs -7.9 mm Hg, respectively; $p<0.02$). At week 12, reductions in trough mean seated diastolic and systolic blood pressure were greater with irbesartan treatment than with losartan treatment (-13.8 mm Hg vs -10.8 mm Hg; $p<0.002$, and -18 mm Hg vs -13.9 mm Hg; $p<0.02$). A greater proportion of irbesartan patients responded to therapy (ie, trough seated diastolic blood pressure < 90 mm Hg or reduction in trough diastolic blood pressure ≥10 mm Hg) compared with losartan patients (78% vs 64%; $p<0.01$). Both regimens were well tolerated with no significant differences between treatment groups with respect to adverse event rates. These results are consistent with a previous study[2] suggesting improved short-term blood pressure control with irbesartan as compared to losartan.

Finally, Andersson and Neldam[4] examined blood-pressure response in mild-to-moderate hypertensive patients randomized to one of four treatment groups:

1. placebo (n=85);
2. losartan (50 mg, n=83);
3. candesartan (8 mg, n=82); or
4. candesartan (16 mg, n=84).

Diastolic blood pressure was significantly lower among the two candesartan groups ($p=0.013$, candesartan 16 mg vs. losartan 50 mg; $p<0.001$, candesartan 8 mg or 16 mg vs. placebo).

Further study is needed to determine whether these differences will be clinically meaningful in the chronic treatment of hypertension for control of blood pressure and prevention of target organ damage.

Summary

A-II contributes to the pathogenesis of hypertension, arterial disease, cardiac hypertrophy, heart failure, and diabetic renal disease.[5] The efficacy of ACE inhibitors in some cardiovascular and renal diseases has encouraged the development of drugs to inhibit the RAS. The newest agents are specific antagonists of A-II receptors. This group, including candesartan, appears to lower blood pressure as effectively as other well-established agents, e.g., diuretics, beta-blockers, and ACE inhibitors, and has a side-effect profile that is similar to that of placebo.

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