Review

Angiotensin Receptor Blockers: How Important Is Selectivity?

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During the last decade, angiotensin-receptor blockers have established themselves as effective antihypertensive agents with impressive safety profile and placebo-like tolerability. Additionally, these compounds provide benefits beyond the reduction in blood pressure, in conditions such as heart failure and in patients with type 2 diabetes and renal insufficiency. It is tempting to group all angiotensin-receptor blockers together as a class, but a closer look reveals differences, for example, in chemical structure, metabolism, dissociation rates, and receptor affinities. Recent findings on the respective roles of the angiotensin receptors AT1 and AT2 have raised the possibility that the degree of selectivity for AT1 over AT2 might affect the performance of the drug. This review attempts to put the concept of selectivity in context and to assess the potential benefits in different organs, with focus on the kidney, endothelium and the heart. Am J Hypertens 2002;15:1006–1014 © 2002 American Journal of Hypertension, Ltd.

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All through history, humans have had a great love of grouping and classifying. This is a legitimate way to structure and make sense of our world, but it is no guarantee of objectivity or of the best possible use of resources. In medicine, frequently, medications are treated as classes by both practitioners and researchers, without taking into account pharmacologic differences between them that may or may not translate into clinical differences.

A good example of a class of drugs in which the members are dissimilar enough to have widely differing effects when studied in clinical trials, are the β-blockers. Although all β-blockers block the β1-adrenergic receptor, they differ in many respects, such as affinity for other adrenergic receptors or in intrinsic sympathetic activity.1 Such differences have turned out to be of clinical significance, as demonstrated in large-scale trials, which have led to the recommendation of only three specified agents: metoprolol, bisoprolol, and carvedilol—not β-blockers as a class, for treatment of heart failure.2,3

If, despite the strong distinguishing pharmacologic and clinical data available, β-blockers are still often treated as a class, it is not surprising that the same is true for many other drug groups. Prominent among these are the angiotensin II receptor blockers (ARBs)—agents that have been greeted as the successors to angiotensin converting enzyme (ACE) inhibitors in the treatment of hypertension. As ACE inhibitors have been the mainstay of therapy for the last 20 years, displacing them would be no mean feat of the ARB. Among the agents poised to take over are losartan, valsartan, candesartan cilexetil, irbesartan, and telmisartan. More drugs based on the same concept are in development.

ARB and ACE Inhibitors

As a class, ARB differ from ACE inhibitors in fundamental ways. Both classes interfere with the action of angiotensin II (Ang II), the principal effector hormone of the renin-angiotensin system (RAS). Ang II has vasoconstrictor and antinatriuretic properties that are important for maintaining blood pressure (BP) and sodium and water homeostasis.4 Ang II is different from all other vasopressor hormones in its self-potentiating and cumulative effect.5 Stimulation by Ang II shifts the pressure–natriuresis curve to the right both acutely and chronically, which has a profound effect on BP long term.6,7

Ang II can act both as a circulating and as a locally produced hormone. As a circulating hormone, Ang II is produced by the ACE, but locally acting Ang II can be synthesized both by ACE and through alternative pathways (for example, by chymase).8 The enzymes in the alternative pathways are not sensitive to ACE inhibitors. Recently, a second variety of chymase has been discovered in human heart tissue.9 This further demonstrates the...
complexity and the variety of enzymatic systems involved in Ang II synthesis and action.

Although the ACE inhibitors block the synthesis of Ang II from its precursor Ang I by inhibiting the actions of ACE, ARBs act directly on the Ang II AT1 receptor. This inhibition takes place at the site of Ang II action and is thus independent of enzymatic pathways for Ang II generation. The ARB do not interfere with bradykinin metabolism, in contrast to ACE inhibitors, which inhibit the kininase activity of the ACE. This is the basis for the well-known clinical observation that use of ACE inhibitors is associated with a dry cough, reported in up to 20% of patients and, in some ethnic groups such as Asians, in as many as 50% of patients.10,11

It is clear that blocking the RAS through ACE inhibition is a crude approach in comparison with ARBs, which act directly at the Ang II receptor. As a class, ARBs are clearly effective at reducing BP in patients with essential hypertension. Their efficacy has been demonstrated in individuals of both sexes and all ages and ethnic backgrounds.12–14 The tolerability profile of ARBs is unsurpassed among antihypertensive agents.15

Differences Among ARBs

Despite the consistent reports of efficacy and tolerability, there are clear differences among ARBs. Structurally, most members of this class (such as losartan, valsartan, candesartan, and irbesartan) include a biphenyltetrazole moiety (Fig. 1), which is believed to aid in positioning the molecule and presenting the active component to the AT1 receptor.16 The biphenyltetrazole unit is attached to different substituents in each agent. Telmisartan and the recent addition eprosartan do not contain the biphenyltetrazole moiety. The active part of the molecule differs among all ARBs; losartan carries a heterocycle imidazole, which, in the case of valsartan, is replaced by a nonplanar acylated amino acid. Such major differences suggest a scope for wide differences in pharmacologic properties among ARBs.

Another difference is the fact that losartan and candesartan cilexetil must be metabolized to become active, in contrast to other members of the group. Candesartan cilexetil is completely converted into the active metabolite candesartan during gastrointestinal absorption. Losartan is not a prodrug in the narrow definition of the word, as the unmetabolized substance has some AT1-antagonistic activity on its own. In vivo, about 15% of the administered drug are converted into the metabolite EXP3174, which has about 10 times the potency of losartan itself.17

Other reported differences between ARBs are affinity for the AT1 receptor and dissociation rate (“staying power”). Most members of the class have AT1-receptor affinities in the nanomolar range (0.6 for candesartan, 2.4 for valsartan, 1.2 for EXP3174, and 5 to 50 for unmetabolized losartan).18–20 These numbers are not entirely comparable, as measurements have been carried out in different tissues. Differences in dissociation rates are more marked. In isolated rat vessels, valsartan and candesartan both have an AT1-dissociation rate of about 1 h, compared with only 2.5 min for losartan.21

Possibly the most important difference between members of the class is their degree of selectivity for the AT1
receptor. In addition to the AT1-receptor mediated harmful
effects, there are other Ang II receptors such as AT2 that
have the potential to do good. The outcome of Ang II
action will depend on which receptor is stimulated. As has
become clearer in recent years, AT2-receptor stimulation
may bring additional benefits to the effects from AT1
blockade, and these benefits could be greater with more
selective agents.

**Ang II Receptors**

The AT1 and AT2 receptors mediate the main actions of
Ang II. The relative abundance of AT1 and AT2 receptors
appears to vary between species, as well as within the
same species depending on state of development. As a
rule, the ratio of AT1/AT2 is >1. An additional receptor,
AT4, which is quite distinct in pharmacology and distri-
bution from the other receptors, has been described—
primarily in the brain, where it seems to be involved in the
regulation of cerebral blood flow and, possibly, with learn-
ing processes. Both the AT1 and AT2 receptors belong to the family of
G-protein coupled receptors, with seven transmembrane
domains and several phosphorylation and glycosylation
sites. The Ang II-binding sites are in the N-terminal
eextracellular domain and in the second extracellular loop,
whereas the antagonist-binding sites are located within the
transmembrane regions.

The AT1 receptors are well conserved between species. The human version is approximately 95% identical to the
rat and bovine AT1 receptors. AT2 receptors are similarly
well conserved, with 99% sequence identity between
rat and mouse and 72% identity between rat and human.
The differences between AT1 and AT2 receptors are far
greater: there is not more than 24% to 33% sequence
identity at the amino-acid level. Most of this identity is
found in the transmembrane domains, where some specific
residues are preserved that are thought to be important for
Ang II binding.

The two receptors also differ in their signal-transduc-
tion pathways. The AT1-mediated signal transduction is
through G-protein activated phospholipase C, D, and A2,
which leads to the generation of 1,2-diacylglycerol (DAG)
and inositol-1,4,5-triphosphate (IP3). Synthesis of IP3
leads to the release of intracellular calcium, which elicits
responses such as aldosterone secretion and vasoconstric-
tion. The substance DAG activates protein kinase C and
calcium-calmodulin kinases, which can activate a variety
of kinases (eg, MAP kinase, STAT 91) in a phosphoryla-
tion cascade.

In contrast, an interesting property of the AT2 receptor
is that although it has the basic structural features of
G-protein coupled receptors in common with AT1, it does
not seem to share any functional characteristics of these
receptors. Instead of mediating signal transduction via
phospholipases and modulating intracellular calcium lev-
els, the AT2 receptor stimulates the production of nitric
oxide (NO), which in turn increases cyclic guanosine
monophosphate (cGMP) production (Fig. 2).

By far, the most thoroughly investigated of the Ang II
receptors is AT1. One reason is that it is more widely
distributed and more strongly expressed than AT2. AT1 is
found in the heart, endothelium, vascular smooth muscle,
brain, platelets, monocytes, several parts of the kidney
(gomeruli, mesangium, proximal tubular epithelium,
medullary interstitium), adrenal cortex, adrenal medulla,
sperm cells and placenta. Stimulation of the AT1 receptor
mediates protein synthesis and cellular growth, and

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**FIG. 2.** Changes in mean (± SEM) renal interstitial fluid cyclic guanosine monophosphate (cGMP) levels in response to intravenous treatment with 0.02 mmol/kg of losartan (L) or valsartan (V). Hatched bars indicate baseline values; solid bars indicate renal interstitial fluid cGMP levels after 1.5 h treatment. Section sign indicates *P < .05* for difference from baseline; double section sign indicates *P < .0001* for differences both from baseline and from losartan-treatment induced cGMP increase.
mitogenic activation is seen after prolonged exposure of AT2 to Ang II.37 In addition, AT2 stimulation leads to extracellular matrix and collagen accumulation.37,38 Growth factor production,39 endothelin and catecholamine release, as well as activation of the inflammatory response.40 A high-sodium diet leads to increased AT1 receptor expression.41

Until recently, the AT2 receptor (reviewed, for example, by Fogari and de Gasparo42) was relatively neglected by investigators; but the realization of its importance and possible clinically beneficial effects have put AT2 at the focus of recent intense research activity. Expression of the AT2 receptor is high during fetal development; however, in adult tissues, AT2 is present only at limited levels, mostly in the adrenal medulla, kidney, specific brain regions, uterus myometrium, heart, and atretic ovarian follicles. Most work has been done on the role of AT2 in the kidney, where it seems to be intimately involved in mediating diuresis and natriuresis and where many of the actions described in other vessels were first elucidated in renal cells.29,30,43–46 The receptor seems to have an important role in the regulation of blood flow, as it has been detected in endothelial cells and in large and small microvessels throughout the skeletal muscle microcirculation (specifically, of the rat).47

Stimulation of the AT1 receptor has several physiologic effects that seem to oppose those of AT1-receptor stimulation. For example, AT2-stimulation mediates vasodilation, via endothelium-derived release of bradykinins and prostaglandins, which in turn mediate the production of the vasodilator NO.29,46,48,49 Blockade of AT2 in rats enhances the pressor response to Ang II.50 Knockout mice lacking the AT2 receptor also show increased sensitivity to the pressor actions of Ang II, whereas, in contrast, transgenic mice overexpressing AT2 have a decreased sensitivity to AT1-mediated pressor action.51,52 In line with these observations, AT2 knockout mice also show increased BP levels compared with wild-type mice.50,51

There are well established antiproliferative effects from AT2-receptor stimulation after neointimal injury and in coronary endothelial cells.53,54 The AT2 receptor can mediate inhibition of mitogen-activated protein kinase in vascular smooth-muscle cells transfected with the AT2 receptor gene, in PC12W cells, and in neuronal cultures,53,55,56 as well as induce apoptosis.56

The levels of AT1 and AT2 change in pathologic circumstances, such as permanently raised Ang II levels. Treatment of AT2-transfected smooth-muscle cells with Ang II leads to increased AT2 receptor levels.57 Myocytes which are subjected to stretch-induced hypertrophy also show increased AT2 expression.58 Importantly, the failing human heart shows higher AT2/AT1 ratios than healthy hearts,59 and in both animal models and human hearts cardiac AT2 levels are upregulated after myocardial infarction,60,61 when the greatest levels of AT2 expression are seen in fibroblasts in interstitial regions.61

There also appears to be cross-talk between the AT1 and AT2 receptors. The upregulation of AT2 in smooth-muscle cells upon injury is blocked by AT1 receptor blockade.55 The expression of AT2 in endothelial cells is stimulated by Ang II; and, if the AT1 receptor is blocked, AT2-gene expression increases and mRNA breakdown is attenuated.62 Cui et al reported that in fetal vascular smooth-muscle cells, Ang II increased extracellular signal regulated kinase phosphorylation through an AT1-mediated mechanism, which in turn is attenuated by activation of the AT2 receptor.63 Gelband et al have described opposing effects from AT1 and AT2 co-localized on catecholaminergic neurons, suggesting cross-talk between Ang II receptors involved in the neurons’ physiologic activity.64 Doubtless, the examples of cross-talk will continue to multiply as research on AT2 intensifies.

The Concept of Selectivity

The desirable effects of AT2 stimulation suggest that the degree of selective AT1 receptor blockade may influence the degree of benefit from ARB treatment. High selectivity is not necessarily related to high affinity for the AT1 receptor; rather, it is a measure of the differences between the affinity for AT1 and AT2. Apart from leaving the AT2 receptor unblocked, high selectivity is expected to lead to additional AT2 stimulation through the so-called yin–yang effect.65 This term refers to the phenomenon that when the AT1 receptor is blocked, local free Ang II levels will rise, leading to increased concentration of Ang II around the AT2 receptors and to concomitant greater stimulation.69 At the same AT1 receptor affinity, the greater the selectivity, the greater the AT2 stimulation.

Advantages from selective blockade can be expected for several organs, most prominently the endothelium, kidney, and the heart.

Selectivity and the Endothelium

Endothelial dysfunction has in recent years been recognized as a strong indication for disease such as hypertension and atherosclerosis, and may precede the development of vascular disease.66 Endothelial cells are located on the inner lining of blood vessels between circulating blood and the vascular smooth muscle, contributing to BP control, blood flow, and vessel patency. In the endothelium, AT1 receptor stimulation by Ang II leads to endothelin release and vasoconstriction. This action is opposed by AT2 receptor–mediated bradykinin and NO release. Experimental evidence for this role of AT2 was provided by McMullen et al, who demonstrated that in uterine arterial rings from ewes, treatment with an AT2 antagonist enhanced the contractile response to Ang II (P < .05), suggesting that AT2 receptors inhibit the AT1 receptor–mediated effects.45

Further benefits of AT2 stimulation are reduced risk for atherosclerosis. Activation of AT1 receptors is thought to be responsible for stimulated growth of the intimal lining in blood vessels, increased adherence of monocytes to
endothelial cells, and aggregation of platelets. Blocking these effects is a highly desirable outcome in itself, but combining AT₁ receptor blockade with increased AT₂ receptor stimulation has the potential of bringing further benefits. Besides NO-induced vasodilation, AT₂ receptor stimulation can mediate growth inhibition in vascular smooth-muscle cells, coronary endothelial cells, and cardiomyocytes. Also, AT₂ stimulation can induce apoptosis in mouse fibroblasts and endothelial cells. There are preclinical indications for these benefits from selective AT₁ receptor blockade. In atherosclerotic rabbits, treatment with the highly selective ARB valsartan has been shown to lead to enlarged lumen areas and to reductions in intimal lesions of the aorta.

Selectivity and the Kidney

The kidney is probably the organ that has received the most attention from Ang II receptor investigators. There are several potentially harmful effects of AT₁ receptor stimulation in the kidney including reduced glomerular filtration rate (GFR), reduced filtration coefficient, increased natriuresis, vasoconstriction primarily in the efferent arteriole, and decreased medullary blood flow.

For several years, adult kidneys were thought to be devoid of AT₂ receptors, but the recent demonstration of AT₂ expression in glomeruli and also in interstitial cells has led to a total reappraisal of the importance of AT₂. In the kidney, NO plays a role in hemodynamic and excretory functions, and the NO-production mediated by AT₂ is thought to be a major factor in this regulation. Stimulation of the AT₂ receptor is responsible for vasodilation of the afferent arteriole, and AT₂ is closely involved in the control of pressure natriuresis by regulating the degree of sodium reabsorption in the proximal convoluted tube.

A well-known advantage of ARBs over ACE inhibitors is their lack of effect on GFR. Angiotensin converting enzyme inhibition can lead to a reduction in GFR in response to decreased renal perfusion. However, the distribution of AT₁ and AT₂ receptors is such that selective AT₁ receptor blockade leads to AT₁ blockade-induced vasodilation in the efferent arteriole and AT₂ stimulation-mediated vasodilation in the afferent arteriole. The net effect is to compensate for the lower GFR caused by the reduction in renal perfusion. This has been seen in animal models with ARBs, and there are studies indicating that the same is true for humans.

Additional renal benefits from selective blockade of the AT₁ receptor seem to be possible in diabetic patients. Nephropathy is a major cause of morbidity and mortality in diabetes mellitus; and much of the harm done to the kidney can be linked to Ang II action and to the independence between the development of hypertension and nephropathy in diabetes. Early renal changes in diabetes include hypertrophy of glomerular and tubular structures. With advancing disease, there is development of tubulo-interstitial fibrosis and renal atherosclerosis, which increases with greater disease severity. Such progression has been associated with Ang II and the AT₁ receptor, particularly with the AT₁-mediated induction of growth factors. Both high glucose levels and Ang II stimulate expression of transforming growth factor-β and synthesis of collagen type IV. Although these effects are reduced by AT₁ receptor blockade, they would also be directly antagonized by AT₂ receptor-mediated effects, such as collagen breakdown and reduced cell proliferation.

There are reports from treatment with ARBs that indicate benefits beyond the reduction in BP. In experimental diabetes in rats, the highly selective ARB valsartan given over 24 weeks attenuates the glomerular ultrastructural changes and prevents the development of albuminuria that is normally observed in this model. In transplant recipients, there is evidence that AT₁ receptor blockade may be better at preserving renal allograft structure and function, as well as increasing recipient survival, than other antihypertensive medication currently used to control BP.

Three independent studies in patients with type 2 diabetes have recently presented data supporting the benefits on kidney function from ARB treatment. Wheelon and Viberti studied BP-independent effects of valsartan treatment on urinary albumin excretion rate in comparison with amlodipine treatment. A total of 332 patients aged 35 to 75 years, with or without hypertension, were randomized to receive either valsartan 80 mg daily (n = 169) or amlo dipine 5 mg daily (n = 163) for 24 weeks. At doses which produced equal reductions in BP, the percentage change from baseline in urinary albumin excretion rate at week 24 was significantly (P < .001) greater for valsartan (−44%) than for amlodipine (−8%). Also, significantly more patients returned to normoalbuminuria status with valsartan treatment than with amlodipine (29.9% vs 14.5%; P = .001).

Other large studies such as Irbesartan Diabetic Nephropathy trial (IDNT). Irbesartan Microalbuminuria (IRMA II), and Reduction of Endpoints in NIDDM with the A-II Antagonist Losartan (RENAAL) have also indicated renal benefits from ARB treatment beyond the reduction in BP. The IDNT studied the effects of the ARB irbesartan compared with amlodipine or placebo in hypertensive patients with type 2 diabetes and nephropathy. The trial reported that the risk of a doubling of the serum creatinine concentration was 33% less in the irbesartan group than in the placebo group (P = .003) and was 37% less in the irbesartan group than in the amlodipine group (P < .001). The relative risk of end-stage renal disease was 23% less in the irbesartan group than in both other groups (P = .07). The RENAAL study, which was conducted in patients with type 2 diabetes and nephropathy who received losartan (in addition to usual antihypertensive treatment if hypertensive), found that losartan reduced the time to end-stage renal disease (28% risk reduction, P = .002) and doubling of serum creatinine (25% risk reduction, P = .006) compared with placebo.
The level of proteinuria declined by 35% with losartan (P < .001 for the comparison with placebo). Similar benefits were seen in the IRMA II trial, in which irbesartan was compared with placebo in patients with type 2 diabetes and microalbuminuria.86

**Selectivity and the Heart**

In the failing heart, Ang II is a major factor in the processes of cardiac remodeling, and the synthesis of vascular ACE is upregulated in heart failure.87,88 The close involvement of Ang II in the development of cardiac hypertrophy has been shown in vivo by Paradis et al.89 Transgenic mice harboring cardiac myocytes that overexpress Ang II displayed significant cardiac hypertrophy and remodeling, with increased interstitial collagen formation and expression of ventricular atrial natriuretic factor. The local Ang II overexpression had no effect on systolic BP or heart rate. In rats, ARB treatment attenuates left ventricular dilation after myocardial infarction.90 One well described AT1-mediated effect is the induction of collagen synthesis, which can be completely inhibited by ARB treatment.91

Regarding the effect of AT2 stimulation in cardiac tissue, experimental results seem promising but definite proofs are still lacking. There are strong indications that the AT2 receptor has the effect of mediating collagen breakdown. Chronic AT1 receptor blockade stimulates collagenase activity, as Varo et al92 could show for the left ventricle of hypertensive rats. Recent data by Wu et al93 on the role of AT1 and AT2 in cardiac remodeling in mice, demonstrate that valsartan administration reduces the damage from pressure-induced cardiac remodeling, not only through blocking AT1 but also through stimulating the AT2 receptor, which led to inhibition of coronary artery thickening and perivascular fibrosis. Similarly, the cardioprotective effects of valsartan are significantly smaller in AT2 receptor knockout mice.

**Comparisons Among ARBs**

These data all speak for ARBs. But do they speak for ARBs as a class? There have been very few direct comparisons of selectivity between ARBs, partly because of differences in measuring such a parameter.

Current data give an indication of selectivity differences. The affinity of losartan for the AT1 receptor is about 1000 times greater than its affinity for AT2 receptors.94 The affinity of telmisartan for the AT1 receptor is more than 3,000 times greater than its affinity for the AT2 receptor.95 In the case of irbesartan the difference is >8500 times greater.96 and candesartan has a reported 10,000 times difference between affinities.97 The greatest reported difference in affinities for AT1 and AT2 is reported for valsartan, at a 30,000 times greater affinity for the AT1 receptor than for the AT2 receptor.20,98

However, these are not direct comparisons and at best give only a hint of in vivo selectivity differences. A sensitive proxy for selectivity is the level of changes in renal cGMP, which can be measured directly.30,49 Renal cGMP is produced in response to several stimuli including bradykinin, which in turn is mediated by AT2 receptor stimulation.45,48,49,99 The absence of additive inhibition of cGMP during combined AT1 receptor blockade and NO-synthase inhibition indicated that the increase in cGMP is mediated solely by the AT2 receptor.

Using this method, the effects of equipotent doses of losartan or valsartan on AT2 receptor mediated renal cGMP allowed a comparison among these ARBs. In this study, time was allowed for losartan to be converted into its active metabolite EXP 3174.

Two major differences between valsartan and losartan were manifest in this study. Valsartan showed a greater potency and selectivity for the AT1 receptor, as indicated by the greater synthesis of Ang II. Valsartan also had markedly longer duration of action. The latter effect probably reflects the differences in dissociation constants favoring valsartan. Valsartan administration led to fivefold greater increases in renal interstitial fluid cGMP from baseline that lasted throughout the study period of 8 h. No such long-lasting effect was seen with losartan. Administration of losartan had practically no effect on cGMP levels 8 hours after administration. All effects on renal interstitial fluid cGMP levels were independent of the effects on BP, which were similar for both ARBs.100

These studies are, of course, far from exhaustive, but they make two points. One is that there are indeed significant differences between ARBs in terms of potency and selectivity. The second is that these differences can be quantified. To decide whether differences in degree of selectivity between members of the ARB class will translate into differences in clinical outcome would presumably need large cardiovascular trials. All ARBs are good at immediately reducing BP and if selectivity differences have clinical relevance this would probably be over long term.

No morbidity/mortality trial has been carried out comparing long-term effects of different ARBs. However, the β-blocker trials have taught us that clinical outcome is not always predictable from pharmacologic differences, and it seems safest not to treat members of drug classes as clinically identical until they have been proved to be so.

**References**

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