Angiotensin II type 1 receptor blockers: Class effects vs. Molecular effects

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Abstract

Highly selective angiotensin II (Ang II) type 1 (AT_1) receptor blockers (ARBs) are now available. AT_1 receptor is a member of the G protein-coupled receptor (GPCR) superfamily and block the diverse effects of Ang II. Several ARBs are available for clinical use. Most ARBs have common molecular structures (biphenyl-tetrazol and imidazol groups) and it is clear that ARBs have "class effects". On the other hand, recent clinical studies have demonstrated that not all ARBs have the same effects, and some benefits conferred by ARBs may not be class effects, and instead may be "molecular effects". In addition, each ARB has been clearly shown to have molecular effects in basic experimental studies, and these effects may be due to small differences in the molecular structure of each ARB. However, it is controversial whether ARBs have molecular effects in a clinical setting. Although the presence of molecular effects for each ARB based on experimental studies may not directly influence the clinical outcome, this possibility has not been adequately evaluated. This review focuses on the class effects vs. molecular effects of ARBs from bench to bedside.

Keywords

Introduction

Angiotensin II (Ang II) is the major effector peptide of the renin-angiotensin system (RAS). Ang II binds to two receptor subtypes Ang II type 1 and type 2 (AT_1 and AT_2) receptors, which are members of the G protein-coupled receptor superfamily (GPCRs). AT_1 receptor blockers (ARBs) are highly selective for the AT_1 receptor and block the deleterious effects of Ang II, such as vasoconstriction, aldosterone release, retention of sodium and water, sympathetic nerve activation and cell proliferation (1). Many ARBs are available for clinical use worldwide. Most ARBs have class (or common) effects because they have common molecular structures [biphenyl-tetrazol and imidazol groups (2)], although recent clinical studies have demonstrated that not all ARBs have the same effects and some benefits conferred by ARBs may not be class effects, but rather molecular (or differential) effects. Each ARB has been shown to have molecular effects in basic experimental studies, and these effects may be due to small differences in the molecular structure of each ARB. The molecular effects most likely may be caused by specific off target effects. However, it is still

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controversial whether each ARB has molecular effects in a clinical setting. Therefore, this review focused on the class effects vs. molecular effects of ARBs in the field of translational research.

Structures of Ang II and AT$_1$ receptor

Ang II is an octapeptide hormone that binds to AT1 receptor, which contains 359 amino acids and has a molecular mass of 41 kDa, by 4 main unique interactions. Two salt bridges, one between the Ang II side-chain Arg[2] and the AT$_1$ residue Asp[281] and the other between Ang II α-COOH group of Phe[8] and the AT$_1$ residue Lys[199], may be important for docking the hormone to the receptor (3,4). These salt-bridge interactions do not play a role in AT$_1$ receptor activation. In addition, we have shown that two important interactions, one between Phe[8] of Ang II and His[256] in AT$_1$ receptor (5) and the other between Ang II Tyr[4] and Asn[111], are necessary to activate the receptor (6,7).

Molecular structures of ARBs

Seven kinds of ARBs are available for clinical use worldwide. Although several peptide types of ARBs have been synthesized since the 1970's, there have been problems with low bioavailability, short duration of action, and partial agonistic activity. The nonpeptidergic ARB losartan was the first to be developed based on imidazole analogues, and was designed by computational modeling (8). Various improved ARBs have been developed since losartan. For example, the chloride group of losartan was changed to a cyclopenthyl group to give irbesartan. Olmesartan contains a hydroxyl group in addition to a α-carboxyl group in the imidazol ring. Since ARBs mimic Ang II, most, including losartan, have common molecular structures (Figure 1), and it is clear that ARBs have class effects.

Binding affinities of ARBs

The K$_d$ values of 7 ARBs and Exp3174, which is an active metabolite of losartan, are shown in Figure 2 (our unpublished data). The K$_d$ values of AT$_1$ receptor binding were determined by ^{125}I-[Sar[1], Ile[8]]Ang II-binding experiments under equilibrium conditions, and binding kinetics values were determined. Irbesartan showed the lowest K$_d$ value, indicating that irbesartan may have the highest binding affinity to the AT$_1$ receptor among these 8 ARBs. In particular, since irbesartan contains a cyclopenthyl group instead of the chloride group in both losartan and Exp3174, irbesartan may show higher binding affinity than these two ARBs. Interestingly, the results of computational modeling have suggested that the cyclopenthyl group of irbesartan may bind to a hydrophobic pocket in the AT$_1$ receptor (Figure 3) (9). In addition, since hydrophobic interaction may occur between the cyclopenthyl group of irbesartan and the AT$_1$ receptor using mutagenesis studies (our unpublished data), we refer to this interaction as "pentagon attachment". Thus, a small difference in the molecular structure may influence various binding affinities.

Fabia et al. studied 36 reports in which blood pressure (BP) was measured using ambulatory BP monitoring for at least 24 hours (10). The antihypertensive activities of ARBs differed, and the magnitude of the reduction in BP did not essentially depend on the initial BP values or on the dose used. In addition, the reduction in mean 24-hour systolic BP with olmesartan was significantly greater than the reductions with losartan and valsartan and equivalent to the reduction with irbesartan (11). On the other hand, magnitude of BP reduction was significantly greater for patients who received olmesartan, but not other ARBs including irbesartan, than for those who received enarapril. Thus, not all ARBs may have the same antihypertensive effects. Although it is natural that the results regarding binding affinities as a molecular effect were not always consistent with those regarding antihypertensive effects,

olmesartan and irbesartan showed better binding affinities than the others, and these ARBs may also be better at lowering BP.

Receptor selectivity and insurmountability of ARBs

All ARBs expect for losartan are highly selective for the AT_1 receptor. In fact, ARBs show 10,000–30,000 times greater affinity for the AT_1 receptor than for the AT_2 receptor. This high selectivity implies that the AT_2 receptor may be exposed to a higher concentration of Ang II because of renin-angiotensin feedback loop after ARBs treatment. Although AT_2 receptor function is still unclear, Ang II-induced AT_2 receptor stimulation may cause anti-cell proliferation and vasodilation (12). Surmountable and insurmountable antagonism largely correspond to competitive and non-competitive antagonism. Although losartan acted as a surmountable antagonist in isolated rat aorta, it acts like an insurmountable antagonist in other models (13). All other ARBs are insurmountable antagonists (14). In addition, compared to telmisartan, olmesartan showed a higher degree of insurmountability for AT_1 receptor (15). However, since insurmountable antagonists overcome the binding of antagonists to the AT_1 receptor only at a high plasma concentration of Ang II, this may not be relevant for the clinical application of ARBs.

Inverse agonism of ARBs

More than 60 wild-type GPCRs have been found to exhibit constitutive activity (16). In most cases, significant levels of constitutive activity are seen in recombinant systems in which GPCR expression levels are relatively high. Although spontaneous mutations have not been reported for the AT_1 receptor, we reported that the WT AT_1 receptor shows slight but significant constitutive activity (17). An inverse agonist can inhibit the constitutive activity of AT_1 receptor. We previously reported that olmesartan and valsartan are stronger inverse agonists than losartan against inositol phosphate production using constitutively active N111G AT_1 mutant receptor (17,18). Although WT AT_1 receptor shows only slight constitutive activity, Morisset et al. clearly showed that inverse agonists are useful in a therapeutic strategy even if non-mutated receptors are expressed at normal levels in GPCRs, H_3 receptor (19).

AT_1 receptor mRNA levels were upregulated by myocyte stretching over time; significant increases were evident 6 hours after stretching, maximal levels (2.8-fold) were observed at 12 hours, and these effects were sustained for up to 18 hours (20). In addition, a recent study demonstrated that the AT_1 receptor is activated by the mechanical stretching of cultured rat myocytes (21,22) and constriction of the transverse aorta in angiotensinogen knockout mice (21) without the involvement of Ang II, and these adverse effects were suppressed by an inverse agonist. Candesartan had greater effects than losartan. In this way, an inverse agonist for the AT_1 receptor may have pharmacotherapeutic relevance, as a molecular effect, for preventing progression of the disease because it takes several decades for hypertension to progress to cardiovascular disease (23).

Several clinical trials have evaluated the effects of ARBs on morbidity and mortality in patients with heart failure (HF). The ELITE II trial suggested that treatment with losartan is not superior to treatment with captopril (24). In the CHARM trial, the benefits of candesartan were demonstrated in patients with HF (25). Although there are important differences in the design and hypotheses of these trials that must be taken into account when comparing their results and interpreting their clinical impact, we should also consider whether these are class effects of ARBs. The inverse agonistic activity of ARBs might also be important for their efficacy in the long-term treatment of heart disease, such as HF including cardiac remodeling, independent of blood pressure-lowering. Although most ARBs have been developed, most ARBs have been simply classified as antagonists. It may

important to classify ARBs with regard to their capacity for inverse agonism as a molecular effect.

Anti-inflammatory effects of ARBs

Ang II induces inflammation in vasculature and vascular remodeling, and subsequently promotes atherosclerosis. Ang II stimulates monocyte chemoattractant protein-1 (MCP-1) (26), interleukin (IL)-8, tumor necrotic factor-α and IL-6 production. Irbesartan inhibited basal MCP-1 production in a dose-dependent manner in human monocytes (27). A similar effect was seen with losartan, at concentrations that were twice as high as those with irbesartan. These previous studies also showed that irbesartan decreased basal MCP-1 levels possibly through a mechanism that was independent of binding to the AT_1 receptor.

The adipose-specific protein adiponectin has been recently discovered to improve insulin sensitivity and inhibit inflammation. Adiponectin protein expression was markedly stimulated by Ang II, which was inhibited by blockade of the AT_2 receptor, and further enhanced by irbesartan (28). Irbesartan-mediated upregulation of adiponectin started beyond the concentrations needed for AT_1 receptor blockade and was also present in the absence of Ang II, which suggests that an AT_1 receptor-independent mechanism of action may be involved. Telmisartan also stimulated adiponectin protein expression, whereas the non-peroxisome proliferator-activated receptor (PPAR)γ-activating eprosartan had no effect. ARBs have molecular effects against MCP-1 production and PPARγ activation, and these effects may not be mediated by AT_1 receptor. There may be another membrane receptor for the irbesartan-induced inhibition of MCP-1 production. Interestingly, both irbesartan and olmesartan may act as antagonists of a theoretical molecular model of C-CChemokine receptor, type-2b (29).

Clinical studies have demonstrated that some ARBs decrease the incidence of new-onset type 2 diabetes (30). In addition, losartan and candesartan increase the plasma levels of adiponectin in patients with essential hypertension (31,32). Although some ARBs have been shown to activate PPARγ, the concentrations used were very high (33,34), and it is doubtful that such concentrations can be achieved in humans. Future large prospective clinical studies that compare PPARγ-activating ARBs to non-activating ARBs will be required to clearly show that a PPARγ-activating phenotype in ARB is superior in patients with type 2 diabetes mellitus and/or hypertension.

Reduction of serum uric acid by ARBs

Generally, ARBs decrease microalbuminuria and proteinuria. With regard to organ protection in the kidney, irbesartan has been studied in two critical large-scale clinical trials [IDNT (Irbesartan Diabetic Nephropathy Trial) (34) and IRMA2 (Irbesartan in patients with type 2 diabetes and microalbuminuria) (35)]. Irbesartan is effective for protecting against the progression of nephropathy due to type 2 diabetes independent of the reduction in BP (35) and has been shown to have a renoprotective effect independent of its BP-lowering effect in patients with type 2 diabetes and microalbuminuria (36). Although the anti-inflammatory effect of irbesartan was stronger than that of losartan, losartan has also been the subject of an important large-scale clinical trial, called RENAAL (37). In that study, losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and although molecular effects did not influence the clinical outcome directly, losartan may have another important molecular effect. Serum uric acid (sUA) is currently recognized as a risk factor for cardiovascular disease as well as chronic kidney disease. Compared to other ARBs, both losartan and irbesartan have been shown to reduce sUA. Interestingly, losartan and telmisartan exhibited cis-inhibitory effects on the uptake of UA by the renal UA transporter (URAT1), and these ARBs reduced uptake in competitive inhibition kinetics (38). On the

other hand, candesartan, Exp3174 (a major metabolite of losartan), olmesartan and valsartan did not have similar inhibitory effects. Such differences in the effects of ARBs on URAT1 could be predicted from the partial chemical structures of ARBs and may involve an AT_1 receptor-independent mechanism of action. The molecular effects of each ARB may be associated with differences in the strength and weakness of the effect of the ARB, and may not reflect the clinical outcome.

Direct comparison of the efficacies on ARBs in clinical trials

Over the past decade, the efficacies of ARBs have been compared and differences were observed, as shown in Table 1, except with regard to BP-lowering. For example, valsartan is more effective than losartan at reducing left ventricular mass index in hypertensive patients (39) and induces greater renal NO production than losartan in hypertensive patients with chronic renal disease (40). Candesartan, but not losartan, significantly lowered plasma levels of plasminogen activator inhibitor type-1 antigen and MCP-1 in patients with hypertension (41). Exp 3174 is the most efficacious ARB at preventing human coronary artery contraction (42). Valsartan decreased the rate of target lesion revascularization after stenting compared to losartan (43). Olmesartan showed a significant reduction of high-sensitive C-reactive protein after stenting compared to valsartan (44). Changes in serum adiponectin and plasma glucose were significantly greater in the telmisartan group than in the candesartan group in patients with both type 2 diabetes and hypertension (45). Although losartan is numerical inferiority in comparison with other ARBs, losartan reduced human platelet activation significantly greater than valsartan and candesartan (46). These differences in the effects of ARBs are independent of BP-lowering in most studies.

Interestingly, when olmesartan was compared to telmisartan, conflicting data were reported (47,48). Although there were no differences between olmesartan and telmisartan with regard to their effects on metabolic parameters including hemoglobinA1c and adiponectin, the decreases in serum IL-6 and hsCRP were more significant with olmesartan (47). On the other hand, telmisartan was more beneficial than olmesartan for improving glucose and lipid profiles (48). Since these trials were relatively small, we must be careful when comparing their results and interpreting their clinical impact, and should also reconsider whether these are molecular effects of ARBs, rather than class effects.

Conclusions

Several clinical trials have shown that ARBs have different degrees of beneficial effects. While most of the benefits conferred by ARBs may be class effects, some may be due to molecular effects. Basic research has clearly demonstrated some molecular effects of ARBs, and an exciting new area in ARB treatment is to determine whether these basic findings can influence the clinical outcome directly or indirectly.

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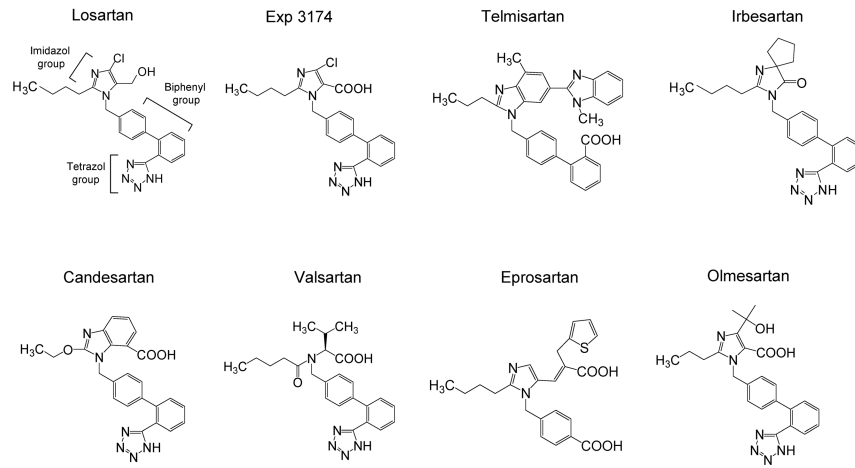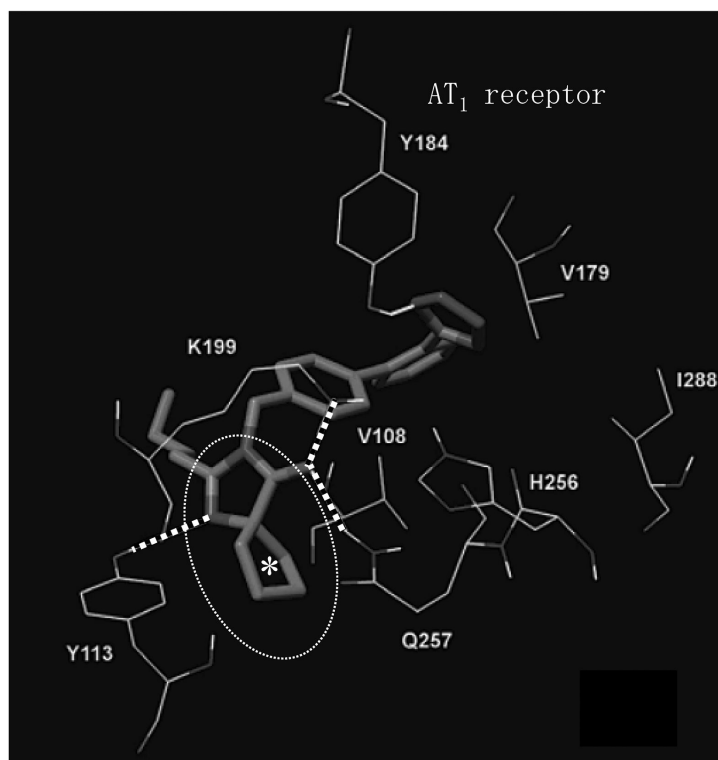
Figure 1.
Molecular structure of 8 ARBs including Exp3174, which is an active metabolite of losartan.
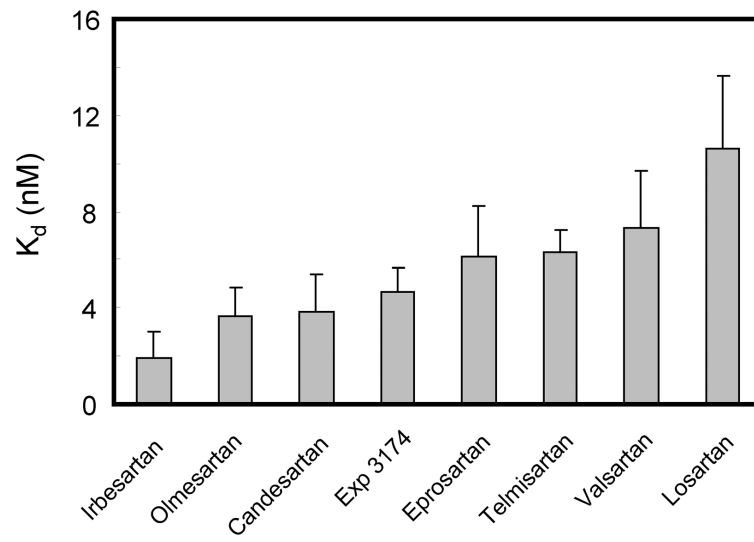
Figure 2.
Binding affinities (K_d) of 8 ARBs including Exp3174, which is an active metabolite of losartan.

Figure 3.
Docking of irbesartan (*cyclopenthyl group) in the AT$_1$ receptor binding site. Interatomic distances between H-bonded atoms are indicated in dotted lines. Dotted circle indicates hydrophobic pocket in the AT$_1$ receptor (*J Med Chem* 2006;49:4305–4316).

Table 1

Direct comparison of the efficacies of ARBs in clinical trials.

Effects	Efficacies	References
Reducing left ventricular mass	valsartan > losartan	39
Increasing nitric oxide production	valsartan>losartan	40
Lowering plasma plasminogen activator inhibitor type-1 antigen and monocyte chemoattractant protein-1	candesartan>losartan	41
Preventing coronary artery contractior	Exp3174>candesartan =valsartan>losartan	42
Preventing coronary restenosis	valsartan>losartan	43
Reduction of C-reactive protein	olmesartan>valsartan	44
Reduction of plasma adiponectin and glucose	telmisartan>candesartan	45
Inhibition of platelet activation	losartan>valsartan >candesartan	46
Reduction of interleukin-6 and C-reactive protein	olmesartan>telmisartan	47
Improvement of glucose and lipid profiles	telmisartan>olmesartan	48