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Pharmacological properties of angiotensin II antagonists: examining all the therapeutic implications

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Abstract

Angiotensin II (Ang II), the effector peptide of the renin-angiotensin system (RAS), exerts a variety of actions in physiological blood pressure and body fluid regulation, and is implicated as a major pathogenic factor in the development of cardiovascular disease. Inhibition of the RAS, via treatment with the angiotensin-converting enzyme inhibitors (ACE-I), or more recently the Ang II AT₁-receptor blockers (ARBs), has been used as a therapeutic approach to the treatment of hypertension and other cardiovascular dysfunction. Evidence from animal and clinical studies shows that the antihypertensive and overall organ-protective actions of the ARBs are similar to those of ACE-I. However, as the ARBs selectively block the AT₁-receptor, which is responsible for the known cardiovascular actions of Ang II, leave the AT₂-receptor unopposed and do not interfere with the breakdown of bradykinin, there is the potential for beneficial effects in hypertensive patients with cardiovascular diseases such as left ventricular hypertrophy. Furthermore, there may be additional benefits when the ARBs are combined with ACE-I in such patients. Animal studies contribute to the elucidation and understanding of the role of AT₁- and AT₂-receptors in the cardiovascular system, and may help in the design of clinical studies aimed at investigating the effects of ACE-I, ARBs, and their combination, on cardiovascular outcomes in hypertensive patients.

Introduction

Angiotensin II (Ang II), the effector peptide of the renin-angiotensin system (RAS), is at the centre of the cardiovascular continuum. Ang II exerts a variety of actions in physiological blood pressure (BP) and body fluid regulation, and has also been implicated as a pathogenic factor, mostly via the Ang II type 1 (AT₁) receptor, at many steps in the development of cardiovascular disease, starting with risk factors such as hypertension and culminating in myocardial infarction (MI), sudden death, and end-stage heart disease. Inhibition of the RAS has therefore been used as a therapeutic approach to the treatment of hypertension and other cardiovascular dysfunction.

The angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE-I) were introduced approximately 20 years ago as antihypertensive agents and have since become one of the most successful therapeutic approaches for hypertension, congestive heart failure, post-MI and diabetic nephropathy. This wide range of indications is a consequence of the fact that ACE-I are thought to possess organ-protective features that go beyond their ability to control BP. In animal experiments, the ability of ACE-I to attenuate the breakdown of kinins, as well as their Ang II-reducing actions, have been shown to contribute to organ protection in various models of cardiovascular disease, including hypertension-induced cardiac left ventricular hypertrophy (LVH) and failure, vascular neo-intima proliferation and media hyper trophy, MI, atherosclerotic vascular disease and the diabetic kidney. In humans, protective effects in diseases such as LVH and diabetic nephropathy, and life-prolonging actions in congestive heart failure, MI and diabetic nephropathy, have been impressively demonstrated in controlled prospective clinical trials. However, it is still not clear whether potentiation of kinin activity contributes to the beneficial effects of ACE-I in patients with these conditions.

Angiotensin II AT₁-receptor blockers

About 10 years ago, the first orally active, selective antagonists of the Ang II AT₁-receptor, the ‘sartans’, were introduced into clinical practice. These drugs differ from ACE-I in that they selectively block one of the Ang II AT receptors, the AT₁-receptor, which is responsible for the known cardiovascular actions of Ang II. They do not interfere directly with kinin breakdown and leave other AT receptors, notably the AT₂-receptor, unopposed.

In animal experiments, the antihypertensive and overall organ-protective actions of the AT₁-receptor blockers (ARBs) are similar to those of ACE-I, and most clinical studies completed so far confirm these observations. These data imply that the reduction of the AT₁-receptor-mediated ‘classical’ effects of Ang II explains not only the antihypertensive but also the organ-protective and potential life-prolonging actions of both ARBs and ACE-I. Evidence from animal experiments suggests the cardiovascular actions of ARBs do involve effects mediated by both Ang II AT₁ and bradykinin B₂ receptors.

Inhibition of the renin-angiotensin system

There are several different pharmacological pathways for influencing the RAS. These include inhibi-
tion of ACE, and selective blockade of Ang II AT₁- and AT₂-receptors. ACE inhibition never completely inhibits the formation of Ang II, since this substance can also be formed from angiotensinogen by non-ACE enzymes. Since ACE also catalyses the breakdown of bradykinin, the latter always plays a role when ACE-I are used, and may possibly be involved indirectly in the effects of the ARBs.

When Ang II binds to the AT₁-receptor, it induces a slight change in receptor conformation. The activated receptor binds to a ‘G-protein’, a GTP-binding protein at the inner side of the cell membrane. A complex signalling cascade, involving protein phosphorylation and intracellular calcium release, is then triggered, culminating in vasoconstriction in vascular smooth muscle cells, growth effects in cells such as cardiomyocytes, vascular smooth muscle cells, or renal mesangioytes, and leading to neuroplasticity in the brain and enzyme activation in liver cells.

Stimulation of the AT₂-receptor produces different effects to those observed for the AT₁-receptor, and include mediation of growth inhibition, tissue regeneration and repair, apoptosis in some cases, and possibly also vasodilatation. These effects have been confirmed in many experimental studies over the last 10 years since the discovery of the AT₂-receptor, although clinical confirmation is still awaited.

In theory, inhibition of the AT₁-receptor, together with stimulation of the unopposed AT₂-receptor, could result in synergistic effects on vasodilatation and growth inhibition. This is supported by experimental evidence accumulated over the last few years.

However, the effects of the AT₁-receptor are only partly ‘physiological’. The RAS is very old in evolutionary terms. It had very important functions in the evolutionary past in helping organisms deal with salt loss, water loss, and reconstitution of the intracellular milieu. But today, when humans generally have enough salt and water for survival, the RAS can generate pathology. Vasoconstriction in vessels may be very important in certain circumstances, but atherosclerosis is certainly not a desirable effect. In the heart, the effects of RAS activation on cell growth may lead to LVH and undesirable arrhythmias. In the kidneys, salt and water retention (which may be important for survival in the desert, but not in everyday life), can turn into a BP-increasing mechanism, and undesirable glomerulosclerosis. In diabetes mellitus, RAS activation may promote diabetic nephropathy. In the brain, RAS activation may be involved in stroke or dementia; we are currently learning a great deal about the effects of central AT₁-receptors.

Regulation of AT₁-receptors following myocardial infarction
The heart has both AT₁- and AT₂-receptors, which may be subject to regulation after ischaemic events such as MI. Animal experiments have shown that one to seven days after an experimental infarct there is a marked up-regulation of both AT₁- and AT₂-receptors (Figure 1). Under normal conditions, only 50% of rat cardiomyocytes contain AT₁-receptors, and about 10% contain AT₂-receptors. However, seven days after experimental infarct there is an increase in the number of AT₂-receptors in rat cardiomyocytes. Other cells in the heart, such as fibroblasts, vessel cells and neuronal cells also contain AT₁- and possibly AT₂-receptors.

Angiotensin II and left ventricular hypertrophy
It has recently become clear that Ang II is a major factor contributing to LVH. Animal experiments indicate that increasing doses of an ARB can
reverse LVH in spontaneously hypertensive rats (Figure 2). Thus, there seems to be a substantial contribution of AT1-receptor stimulation to cardiovascular risk.

**AT1-receptor blockade and free radicals**

Blood vessels are also a target for pathological RAS activation. Vessels are subject to endothelial dysfunction and injury because of the large shear forces that hypertension and Ang II, both independently and in conjunction, exert on the vessel wall. Increased vessel wall thickness and endothelial dysfunction may lead to atherosclerosis via changes in gene expression, lipid metabolism, and the generation of free radicals.

The effects of Ang II and AT1-receptor blockade on the production of reactive oxygen species by the enzyme NADP/NADPH oxidase, which is intimately involved in free radical production and in the generation of atherosclerosis, has been explored experimentally. In this study, one group of rats received an intravenous infusion of Ang II and a second group received noradrenaline. Both groups experienced a similar increase in BP. NADP/NADPH oxidase activity increased in the group that received Ang II but not in the group receiving noradrenaline. The group that received Ang II experienced an increase in BP, NADP/NADPH oxidase activity, and the increase in free oxygen radicals in the Ang II group.

When the AT1-receptor is blocked, unopposed AT2-receptor stimulation may have beneficial effects. In a study using genetically hypertensive rats, AT1-receptor blockade produced elevated production of NO and cGMP in the vascular walls, which was mediated by the AT2-receptor. These results have also been confirmed for the heart and kidney in several other studies. We may speculate that oxygen free radicals would be scavenged by NO, and that elevated cGMP will result in vessel protection and vasodilation.

**Combination of AT1-receptor blockade and ACE inhibition**

The HOPE study has confirmed the beneficial clinical effects of ACE-I in limiting target organ damage. In theory, there may be further benefits when ACE inhibition is combined with AT1-receptor blockade. However, to assess these potential benefits, it must be acknowledged that bradykinin has effects, and that sources of Ang II other than ACE exist. The existence of ACE-independent Ang II-forming enzymes means that ACE blockade of Ang II production is never complete. Also, ARBs completely block AT1-receptors but leave AT2-receptors unopposed, which, in turn, may or may not affect bradykinin levels (Table 1).

ACE-I reduce both AT1- and AT2-receptor-mediated activity since Ang II is a ligand for both receptors. Levels of Ang II will be decreased because ACE is inhibited, and bradykinin levels will be increased. Plasma renin is activated due to the

### Table 1

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decreased negative feedback of Ang II on kidney renin release. In contrast, ARBs produce a more complete antagonism of the effects of Ang II than ACE-I, and there may be some stimulation of the unopposed AT2-receptor. Plasma renin is activated, as with ACE inhibition, Ang II levels are not decreased, as Ang II production is not inhibited. Bradykinin, at least in the plasma, will not be increased.

In theory, the combination of an ARB and an ACE-I will produce the effects of both agents. More or less complete blockade of the AT1-receptor, with less AT2-receptor stimulation than with ARBs alone, as the ACE-I will stop production of some Ang II, would be anticipated. Renin levels will be elevated because there is less Ang II at the kidney and AT1 is blocked, resulting in no negative feedback. Overall, Ang II levels may be unchanged or slightly elevated, depending on the balance of effects of each treatment on Ang II. Bradykinin levels are probably increased because ACE-I inhibit the breakdown of bradykinin.

The acute effects of ARB and an ACE-I, alone and in combination, have been investigated in an experimental study in spontaneously hypertensive rats conducted at this laboratory (T. Unger, personal communication). These rats underwent a permanent ligation of a coronary artery so as to induce an area of MI. This may serve as a model for hypertensive patients treated with RAS-modulating drugs, who subsequently suffer a MI.

Six weeks after coronary artery ligation, there was 90% mortality in placebo-treated rats (and 15% mortality in sham-operated rats). Treatment with irbesartan alone was considerably more effective than with ramipril alone, or the combination treatment, in reducing mortality. The relatively low efficacy of the combination treatment may be explained by the fact that lower doses (by about 50%) of each agent were used than in the monotherapy treatment groups, to prevent possible cardioprotective effects due to further BP reduction.

**Conclusion**

Experimental studies, such as those described above, helped to contribute to our understanding of the role of AT1- and AT2-receptors in the cardiovascular system, and may help in the design of clinical studies aimed at investigating the effects of ACE-I, ARBs, and their combination, on cardiovascular outcomes in hypertensive patients.

**References**