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COMMENTARY

Do all angiotensin II type 1 receptor blockers have the same beneficial effects?

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Angiotensin II type 1 (AT_1) receptor blockers (ARBs) are highly selective for the AT_1 receptor, which is a member of the G protein-coupled receptor superfamily (GPCRs), and block the diverse effects (hypertension, hypertrophy, heart failure, proteinuria etc.) of angiotensin II. Many ARBs are in clinical use and have been shown to be safe and effective. Over the past several years, reports have discussed the different degrees of the beneficial effects of ARBs. As ARBs do not all have the same effects, the benefits conferred by ARBs may not be class effects. These different effects may be due to differences in the molecular characteristics of ARBs. The results reported by Le *et al*. in this issue highlight the different characteristics of two ARBs, olmesartan and telmisartan, and suggest that the higher degree of insurmountability, slower dissociation, and higher affinity of olmesartan compared to telmisartan for AT_1 receptors may help it to form a tight binding complex with this receptor. A better understanding of the different molecular mechanisms for each ARB could be useful for the treatment of patients.
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Abbreviations: Ang II, angiotensin II; AT_1, angiotensin II type 1; ARBs, angiotensin II type 1 receptor blockers; IP, inositol phosphate

The type 1 (AT_1) receptor for the octapeptide hormone angiotensin II (Ang II) is a member of the G-protein-coupled receptor superfamily (GPCRs). The renin–angiotensin system hormone Ang II plays a central role as a major regulator of blood pressure (BP), electrolyte balance and endocrine function related to vascular disease (Miura *et al*., 2003).

Over the past several years, the efficacies of AT_1 receptor blockers (ARBs) have been compared and differences have been observed in their pleiotropic effects as well as in the lowering of BP (Miura *et al*., 2005). The BP-lowering effects of five ARBs used in Japan have been compared to those of the angiotensin-converting enzyme inhibitor enalapril (Arakawa, 2004). The vaso-depressor effects of candesartan, valsartan and telmisartan were greater than those of enalapril, but not significantly. Only olmesartan had a significantly greater BP-lowering effect than enalapril. In addition, Smith *et al*. (2005) reported that olmesartan is significantly more effective than losartan or valsartan for the treatment of hypertension. Regarding the pleiotropic effects of ARBs, decreased renal nitric oxide is reversed more strongly by valsartan than losartan in streptozotocin-induced diabetes rats (Awad *et al*., 2004) and in hypertensive patients with chronic renal disease (Matsuda *et al*., 2003). Koh *et al*. (2004) reported that treatment with candesartan, but not losartan, significantly lowered plasma levels of plasminogen activator inhibitor type-1 antigen and monocyte chemoattractant protein-1 in patients with hypertension. Our clinical trial showed that valsartan significantly decreased stenosis after stent implantation compared to losartan in patients with coronary artery disease (Iwata *et al*., 2007). These reports clearly indicate that the effects of ARBs may not be class effects. Regarding the BP-lowering effect, olmesartan may have a stronger vaso-depressor effect. In addition, losartan has a relatively weak beneficial effect compared to other ARBs. The most important function of ARBs is their receptor antagonism, which can block Ang II-induced signalling. However, olmesartan has strong inverse agonistic actions towards inositol phosphate (IP) production and extracellular-signal-regulated kinase activation independent of Ang II stimulation (we refer to this notion as the 'dual inverse agonism') and, as losartan had only weak actions, the differential effects between olmesartan and losartan might be due to these actions (Miura *et al*. 2003, 2006; Yasuda *et al*. 2005).

In this issue of *British Journal of Pharmacology*, Le *et al*. (2007) add critical new insights regarding the differential characterization of the interactions between olmesartan and telmisartan, such as the degree of insurmountability, dissociation and the affinity of two ARBs. Although both ARBs were found to be competitive antagonists, this *in vitro* study showed that olmesartan had a higher degree of insurmountability, slower dissociation and higher affinity

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than telmisartan for AT_1 receptor. In their washout experiments, [^{3}H]-telmisartan dissociated from the receptor with a half-life of 29.4 min and the Ang II-mediated IP accumulation response was restored to 50% of maximum within 24.5 min, while the values for [^{3}H]-olmesartan were 72 and 76 min, respectively. These data indicate that olmesartan may bind tightly to AT_1 receptor. In fact, our binding assays and molecular model studies suggest that the interactions of the hydroxyl and carboxyl groups in the imidazole core and tetrazole group in the biphenyl moiety of olmesartan with Tyr^{113}, Lys^{199}, His^{256} and Gln^{257} in the AT_1 receptor play important roles in the tight binding between olmesartan and the receptor (Miura *et al*., 2006). On the other hand, telmisartan has a carboxyl substituent instead of a tetrazole group and lacks a heterocyclic substituent of the benzimidazole moiety, with no carboxyl group in the imidazole core (Berellini *et al.*, 2005). In this study, regarding the degree of insurmountability and the dissociation rate, telmisartan is comparable to Exp 3174 (the active metabolite of losartan), which contains a carboxyl group in the imidazole core and a tetrazole group in the biphenyl group, while telmisartan shows lower affinity. Differences in the chemical structures of olmesartan and telmisartan may therefore affect their binding behaviour and IP accumulation response.

Another important finding by Le *et al*. (2007) is that the specific binding behaviour between olmesartan and AT_1 receptor could be described by a two-step process with the initial formation of a loose complex (IR) and subsequent transformation into a tight binding complex (IR*). The initial olmesartan (I) receptor (R) interaction yields a fast reversible/surmountable complex (IR). A biphenyl-tetrazole group that is contained in most ARBs including olmesartan plays a role in this process. The carboxyl group of olmesartan contributes to its insurmountability, and other substituents could further stabilize the IR* complex. We also previously showed that cooperative interactions between the carboxyl group and His^{256} and between the hydroxyl group and Tyr^{113} in the AT_1 receptor were essential for the potent inverse agonist activity of olmesartan (Miura *et al*., 2006). The specific binding behaviour between olmesartan and AT_1 receptor regarding insurmountability or inverse agonism may be similar.

The present study (Le *et al*., 2007) has attempted to elucidate the molecular characteristics that underlie insurmountability, dissociation and affinity of ARBs and provided a new perspective in research on the AT_1 receptor. Although there have been no randomized clinical studies on olmesartan versus telmisartan, a better understanding of the different molecular mechanisms for each ARB could be useful in the treatment of hypertension.

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