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Unique "delta lock" structure of telmisartan is involved in its strongest binding affinity to angiotensin II type 1 receptor

Kazuki Ohno [a], Yasushi Amano [a], Hirotoshi Kakuta [a], Tatsuya Niimi [a], Shoji Takakura [a], Masaya Orita [a], Keiji Miyata [a], Hitoshi Sakashita [a], Makoto Takeuchi [a], Issei Komuro [b], Jitsuo Higaki [c], Masatsugu Horiuchi [d], Shokei Kim-Mitsuyama [e], Yutaka Mori [f], Ryuichi Morishita [g], Sho-ichi Yamagishi [h,*]

[a] Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Japan
[b] Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan
[c] Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Toon, Japan
[d] Department of Molecular Cardiovascular Biology and Pharmacology, Ehime University Graduate School of Medicine, Toon, Japan
[e] Department of Pharmacology and Molecular Therapeutics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan
[f] Division of Diabetes and Endocrinology, Department of Internal Medicine, Jikei University Daisan Hospital, Komae, Japan
[g] Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine, Suita, Japan
[h] Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan

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ABSTRACT

Angiotensin II type 1 receptor (AT1 receptor) blockers (ARBs) are one of the most popular anti-hypertensive agents. Control of blood pressure (BP) by ARBs is now a therapeutic target for the organ protection in patients with hypertension. Recent meta-analysis demonstrated the possibility that telmisartan was the strongest ARB for the reduction of BP in patients with essential hypertension. However, which molecular interactions of telmisartan with the AT1 receptor could explain its strongest BP lowering activity remains unclear. To address the issue, we constructed models for the interaction between commonly used ARBs and AT1 receptor and compared the docking model of telmisartan with that of other ARBs. Telmisartan has a unique binding mode to the AT1 receptor due to its distal benzimidazole portion. This unique portion could explain the highest molecular lipophilicity, the greatest volume distribution and the strongest binding affinity of telmisartan to AT1 receptor. Furthermore, telmisartan was found to firmly bind to the AT1 receptor through the unique "delta lock" structure. Our present study suggests that due to its "delta lock" structure, telmisartan may be superior to other ARBs in halting cardiovascular disease in patients with hypertension.

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1. Introduction

There is a growing body of evidence that blood pressure (BP) level is one of the major determinants of cardiovascular morbidity and mortality in individuals [1]. A recent analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) revealed that any commonly used BP-lowering regimen reduced the risk of total major cardiovascular events, and larger lowering in BP level produced larger reductions in the risk [2]. These observations suggest that most of the differences among treatment regimens in their effects on cardiovascular outcomes could be explained by the differences in achieved BP level.

Angiotensin II (Ang II) is a physiologically active major substance of the renin–angiotensin system (RAS). Furthermore, Ang II exerts various biological effects in blood vessel, kidney and heart via the interaction with type 1 receptor (AT1 receptor) [3,4]. Therefore, inhibition of the RAS by angiotensin-converting enzyme inhibitors and/or AT1 receptor blockers (ARBs) may be a therapeutic target for the organ protection in patients with hypertension [1,5,6]. Recent guidelines of USA and Europe recommend RAS inhibitors as the first-line drugs for the management of patients with chronic kidney disease and/or diabetes [7–9].

There are some differences of BP lowering effects among various ARBs [10,11]. Indeed, recent meta-analysis demonstrated the possibility hat telmisartan was the strongest ARB for the reduction of BP level in patients with essential hypertension [10]. However, which molecular interactions of telmisartan with the AT1 receptor could explain its strongest BP lowering activity remains unclear. To address the issue, in this study, we constructed models for the interac-

* Corresponding author. Address: Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Fax: +81 942 31 7895.
E-mail address: shoichi@med.kurume-u.ac.jp (S.-i. Yamagishi).

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tion between commonly used ARBs and AT1 receptor and compared the docking model of telmisartan with those of other ARBs.

2. Materials and methods

Three-dimensional (3D) structures of seven ARBs (telmisartan, candesartan, valsartan, EXP3174 (active metabolite of losartan), olmesartan, irbesartan and azilsartan) (Fig. 1) were constructed using molecular modeling software Molecular Operating Environment version 2009.1001 (Chemical Computing Group, Inc., Montreal, Canada). 3D model of the AT1 receptor, which was generated using bovine rhodopsin crystal structure as a template as described by Tuccinardi et al. [12], was energy minimized using Molecular Operating Environment version 2009.1001, and then used for our docking studies. Each ARB was docked into the AT1 receptor model using docking program GOLD version 3.2 (CCDC Software Ltd., Cambridge, UK) with default parameter settings.

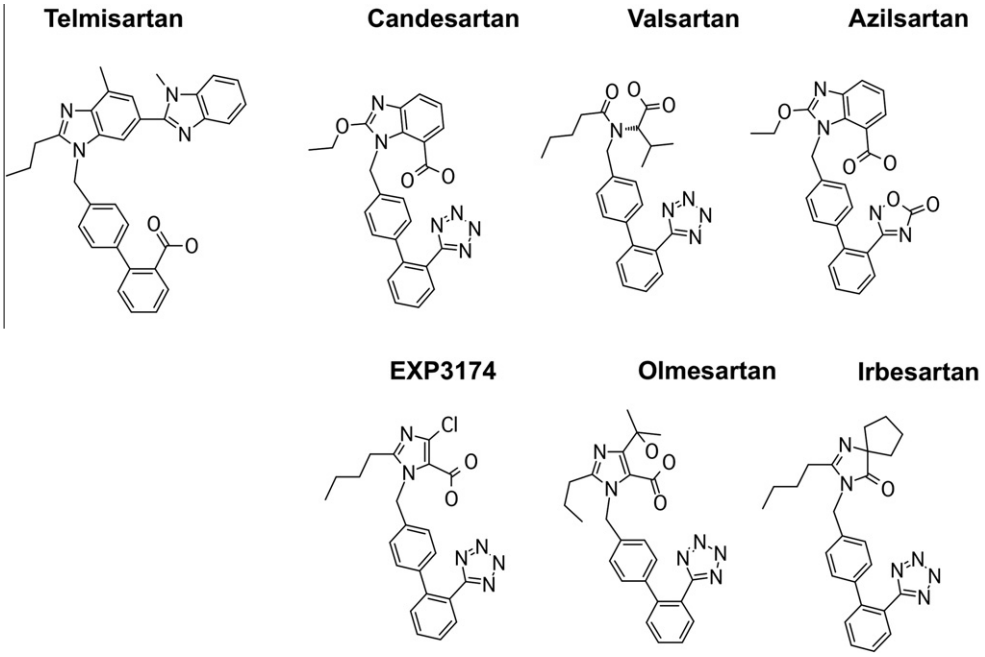

Fig. 1. Chemical structures of telmisartan, candesartan, valsartan, azilsartan, EXP3174, olmesartan and irbesartan.

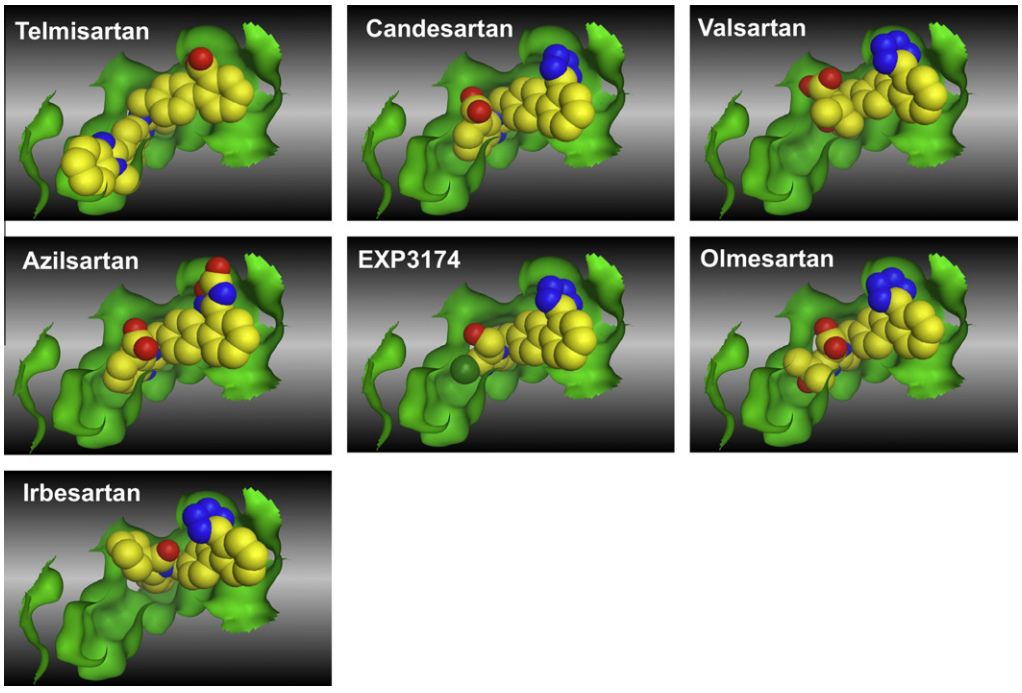

Fig. 2. Predicted binding mode of each ARB to the AT1 receptor binding pocket. AT1 receptor binding pocket is shown as green color. Yellow, blue and red colors indicate carbon, nitrogen and oxygen atoms of each ARB, respectively.

Table 1
Interaction types between each ARBs and AT1 receptor.

Residue	Telmisartan	Candesartan	Valsartan	Azilsartan	EXP3174	Olmesartan	Irbesartan
Phe 171	HC	HC	HC	HC	HC	HC	HC
Phe 182	HC	HC	HC	HC	HC	HC	HC
Tyr 184	HB	HB	HB	HB	HB	HB	HB
Lys 199	Cat–π	SB	SB	SB	SB	SB	SB
His 256	SB	SB	SB	SB	SB	SB	SB
Tyr 113	HB	HB	HB	HB	HB	HB	
Gln 257	HB	HB	HB	HB			
Val 116	HC						
Phe 204	HC						
Phe 208	HC						
Trp 253	HC						

HB, hydrogen bond; SB, salt bridge; HC, hydrophobic contact; Cat–π, cation–π interaction.

3. Results

Fig. 2 shows the predicted binding mode of each ARB to the AT1 receptor. In this figure, AT1 receptor binding pocket is shown as green color. Yellow, blue and red colors indicate carbon, nitrogen and oxygen atoms of each ARB, respectively. As shown in Fig. 2, telmisartan was found to fit most with the binding pocket of AT1 receptor model, whereas fitness of other ARBs was partial and incomplete.

As shown in Table 1, all of the ARBs studied here interacted with Phe 171, Phe 182, Tyr 184, Lys 199 and His 256 residues of AT1 receptor model. Telmisartan was found to be unique; it had additional interaction sites that could bind to hydrophobic residues of ATI receptor, which were composed of Val 116, Phe 204, Phe 208 and Trp 253.

As shown in Fig. 3, the distal benzimidazole portion of telmisartan (portion I) was found to interact with the lipophilic pocket of AT1 receptor model, which was comprised of Val 116, Phe 204, Phe 208 and Trp 253. Further, the central benzimidazole portion of telmisartan (portion II) provided interaction sites that could bind to Tyr 113, Phe 171, Phe 182 and Lys 199, whereas the biphenyl carboxylic acid portion (portion III) interacted with Tyr 184 and His 256 residues of AT1 receptor model.

When we re-performed modeling study using beta-adrenergic receptor crystal structure as a template [13], the results were almost same; the distal benzimidazole portion of telmisartan (portion I) interacted with the lipophilic pocket of AT1 receptor model, which was comprised of Phe 204, Phe 208 and Trp 253. Further, the central benzimidazole portion of telmisartan (portion II) provided interaction sites that could bind to Tyr 113 and Lys 199, whereas the biphenyl carboxylic acid portion (portion III) interacted with His 256 residues of AT1 receptor model (Fig. 4).

4. Discussion

Here, using *in silico* docking studies, we demonstrated for the first time that telmisartan had a unique binding mode to the AT1 receptor. We showed here that among various ARBs, only telmisartan had hydrophobic contacts with Val 116, Phe 204, Phe 208 and Trp 253 residues of the AT1 receptor via its distal benzimidazole domain (Fig. 3, portion I). The docking model of telmisartan to AT1 receptor observed here differed from that reported previously by Patny et al. [14]. The AT1 model structure used for our docking studies was different from theirs, which could explain the discrepant results. However, in contrast to Patny's report, Tyr 113 and Gln 257 were indispensable for the binding of ARBs to AT1 receptor in our model, which was consistent with the previous observation showing that binding affinity of olmesartan to AT1 receptor was dramatically decreased when Tyr 113 and Gln 257 residues were mutated [15]. The finding suggests that AT1 model structure used here is more suitable for docking study.

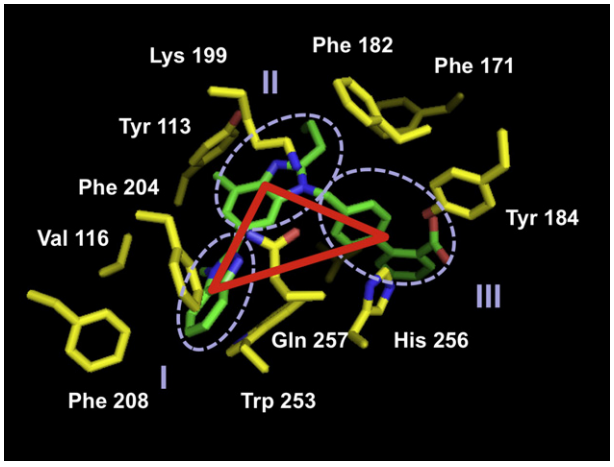

Fig. 3. Docking model of telmisartan to AT1 receptor using rhodopsin crystal structure as a template. Residues in the binding pocket of AT1 receptor model are shown as yellow colors. Green indicates the structure of telmisartan. Telmisartan bound to the AT1 receptor through the distal benzimidazole portion (I), the central benzimidazole portion (II) and the biphenyl carboxylic acid portion (III), which was named here "delta lock" structure (Δ).

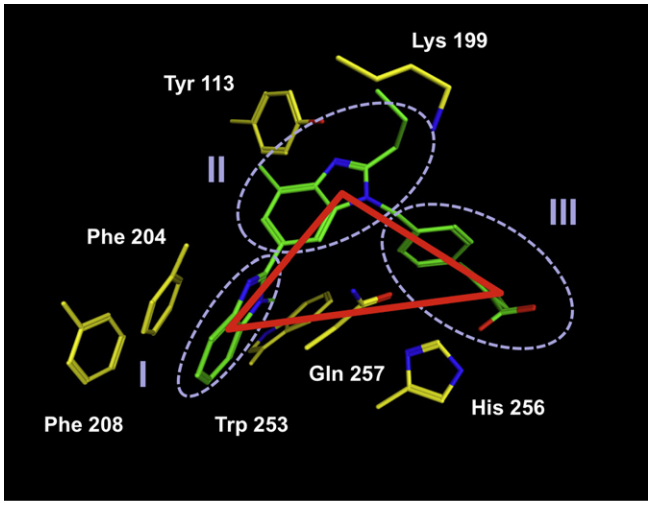

Fig. 4. Docking model of telmisartan to AT1 receptor using beta-adrenergic receptor crystal structure as a template. Residues in the binding pocket of AT1 receptor model are shown as yellow colors. Green indicates the structure of telmisartan. Telmisartan bound to the AT1 receptor through the distal benzimidazole portion (I), the central benzimidazole portion (II) and the biphenyl carboxylic acid portion (III), which was named here "delta lock" structure (Δ).

In the present study, we demonstrated that the distal benzimidazole portion of telmisartan (Fig. 3, portion I) occupied the hydrophobic pocket of AT1 receptor. Thus the highest molecular lipophilicity [16] and greatest volume distribution [17] of telmisartan were ascribed partly to its benzimidazole domain. In addition, telmisartan was found to be a sole ARB that could entirely fill the binding pocket of AT1 receptor and restrict its conformation via its distal benzimidazole portion. Kakuta et al. previously reported [18] that telmisartan had the smallest dissociate constant to AT1 receptor among various ARBs. Thus the unique benzimidazole portion of telmisartan (portion I) could also explain its strongest AT1 receptor antagonizing ability *in vitro* [18].

Since the portion II and III of telmisartan were also involved in its high affinity to AT1 receptor, telmisartan could firmly bind to the AT1 receptor through the portion I, II and III, which were named here "delta lock" structure (Δ in Fig. 3). Recently, Nixon et al. suggested the possibility in their meta-analysis that telmisartan had the strongest BP-lowering effect among various ARBs [10]. Therefore, our present study suggests that unique chemical structure of telmisartan, *that is*, "delta lock" structure may be involved in its strongest binding affinity to AT1 receptor and greatest BP lowering properties *in vivo*. Due to its unique "delta lock" structure, telmisartan may be superior to other ARBs in halting cardiovascular disease in patients with hypertension.

AT1 belongs to a family of G-protein coupled receptor and after previous modeling studies in 2006 [12], now crystal structures of human beta-adrenergic receptor are available from protein data bank [13]. Since not all, but some core part sequence of AT1 is more similar to that of beta-adrenergic receptor than that of rhodopsin and that accuracy of AT1 model is so critical in this study, we re-performed modeling study using beta-adrenergic receptor crystal structure as a template. Modeling study using beta-adrenergic receptor also revealed that telmisartan firmly bound to AT1 receptor through the portion I, II and III (Fig. 4), further supporting the concept that strong binding affinity of telmisartan could be ascribed to its unique "delta lock" structure.

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