Editorial Commentary

Why Do We Need a Selective Angiotensin II Type 2 Receptor Agonist?

Daniel Henrion

See related article, pp 722–729

The renin-angiotensin system has a central role in the regulation of blood pressure and water balance. It is also a main target in the treatment of hypertension. Angiotensin II has 2 major receptors, the type 1 (AT_1R) and the type 2 receptor (AT_2R), both coupled to G proteins. Adverse vascular remodeling observed in cardiovascular diseases is attributed to AT_1R, and a large number of relatively selective AT_1R inhibitors are now used in patients. The effects of AT_2R are usually presented as counteracting the effects exerted by AT_1R. Consequently, some beneficial effects of the AT_1R blockers (angiotensin receptor blocker) are commonly attributed to AT_2R activation.[1] Beneficial vascular effects of AT_2R have now been proven by several studies. For example, AT_2R stimulation reduces vascular RhoA/Rho kinase/myosin light chain phosphorylation in angiotensin II and AT_1R antagonist valsartan-treated vascular smooth muscle cells in vitro, as well as in the aorta of spontaneously hypertensive rats chronically treated with candesartan.[2] Altogether, previous studies suggest a role for vascular AT_2R in blood pressure lowering during chronic AT_1R blockade. Similarly, in hypertensive diabetic patients, chronic angiotensin receptor blocker treatment increases AT_2R expression level and AT_2R-dependent vasodilatation of mesenteric resistance arteries.[3] Nevertheless, in the absence of AT_1R inhibition, expression of AT_2R varies a lot under physiological and pathophysiological conditions,[4] and the relatively low selectivity of the antagonist PD123319 and the weak specificity of the agonist CGP42112 do not help fully understand the role of AT_2R. Thus, its role in most cardiovascular and metabolic disorders remains poorly understood and mainly hypothetical.

Consequently, the availability of the first nonpeptide AT_2R agonist, compound 21 (C21), was seen as a major breakthrough, as described in a recent review article.[1] Indeed, C21 has protective effects after myocardial infarction and in hypertension-induced end organ damage. In different animal models, AT_2Rs also display an anti-inflammatory effect.[1]

Nevertheless, there is accumulating evidence that the commonly accepted scheme with a balance between a constrictor effect of AT_1R and a dilator effect of AT_2R is too simplistic and does not always reflect experimental evidence. The work performed by Verdonk et al,[5] published in this issue of *Hypertension*, on the AT_2R agonist C21 further highlights the complexity of this system, in addition to bringing key information on the mechanism of action of this new drug. Although C21 binds to AT_2R with high affinity, this study also shows that C21 induces a puzzling combination of vasodilation and vasoconstriction. Surprisingly, C21-mediated vasodilation was independent of AT_2R and of the endothelium. Indeed, the authors have shown that C21 has a direct inhibitory effect on calcium influx into smooth muscle cells, thus leading to relaxation. C21 was tested in rat and mouse arteries, as well as human coronary arteries, and C21-dependent vasodilation through calcium entry inhibition was also observed in mice lacking the gene encoding for AT_2R. Furthermore, in the isolated perfused heart, C21 induces an initial AT_1R-dependent contraction followed by AT_2R-independent dilatation. The constrictor effect of AT_2R was more pronounced in hypertensive rats, as shown previously.[6]

This article brings up 2 major issues requiring further discussion. First, C21-dependent dilatation relies mainly on calcium entry blockade without interfering with the RhoA-Rho-kinase pathway, which has been shown to be inhibited after AT_2R stimulation. This finding requires reanalysis of the studies showing protective effects of C21. Indeed, the organ-protective effect of C21 is compatible with the effects of the dihydropyridine calcium channel blockers, that is, reduction of proliferation, inflammation, fibrosis, and vasoconstriction. The authors also show that low doses C21 are needed to selectively block AT_2R. Lower doses of C21 might be used after AT_1R blockade, which induces a large increase in AT_2R expression level. In this condition, lower doses of C21 might be sufficient to more selectively block AT_2R. Lower-dose C21 could, thus, be useful in resistant hypertension, although in this case its effect on calcium currents might also be advantageous. Low-dose C21 might also provide additional protection against organ damage in kidney and heart diseases in patients treated with angiotensin receptor blockers. Nevertheless, no data are yet available to support this assumption. It should be noted that more and more patients, not only hypertensive patients, receive angiotensin receptor blockers. In these conditions, a better knowledge of the effect of AT_2R stimulation is essential, especially in the different organs affected by cardiovascular diseases. Second, this work further confirms with straightforward experiments

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From the Department of Integrated Neurovascular and Mitochondrial Biology, Institut National de la Santé et de la Recherche Médicale U1083, Angers, France; Centre National de la Recherche Scientifique Unité Mixte de Recherche 6214, Angers, France; University of Angers, Angers, France; University Hospital of Angers, Angers, France.

Correspondence to Daniel Henrion, Department of Integrated Neurovascular and Mitochondrial Biology, UMR CNRS 6214-INSERM U1083, University of Angers, 49045 Angers, France. E-mail daniel.henrion@univ-angers.fr

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the complexity of AT_2R physiopathology. That AT_2R stimulation induces dilatation or contraction depending on the type of artery or on the disease makes it difficult to use tools targeting this receptor.

Indeed, the findings of this article raise several important questions, the answers to which await further investigation. First, is there enough AT_2R to be stimulated in the absence of AT_1R blockade or in the absence of other factors increasing AT_2R expression level and, second, is the effect of AT_2R stimulation enough predictable. Although AT_2R do not seem to desensitize, its stimulation does not induce important dilatation, and, in some cases, vasoconstriction may occur as observed in hypertensive[6] or in aged rats.[7] Furthermore, AT_2R-dependent dilatation may be stronger and perhaps more persistent in female than in male rats.[8] However, in the present study, coronary arteries from 2 men and 3 women were used without obvious difference attributed to gender, so more attention should be given in future studies to a possible sex difference in the effects of AT_2R stimulation. Indeed, AT_2R may have a role, other than the estrogen receptors, in the protection against cardiovascular events provided by female hormones before menopause. Of course, this very hypothetical issue remains to be further investigated.

That the effect of AT_2R stimulation varies so much according to tissue type, age, sex, or diseases remains puzzling. Nevertheless, a more direct interaction between receptors may provide, at least in part, an explanation. Indeed, AT_2R-AT_1R dimerization might occur and affect the consecutive signal transduction. Although this concept still lacks functional evidence, receptor dimerization should be taken into account in future studies, especially because it may affect receptor internalization and intracellular signaling. Internalization of AT_2R does not seem to occur, whereas AT_1R internalization follows rapidly its stimulation.[9] Consequently AT_2R-AT_1R heterodimerization might affect, and eventually prevent, AT_1R intracellular signaling. Finally, although the role of internalized AT_1R is not yet fully understood, angiotensin II receptor, AT_1R, AT_2R, and AT_7R, have been identified in the nucleus and in mitochondria.[10] Once again, the AT_2R differs from the other receptors because it lacks the canonical nuclear localization sequence. Nevertheless, in isolated nuclear or mitochondrial fractions, AT_2R stimulation with CGP4211A induces NO production, which is suppressed by PD123319 and by N^G-nitro-L-arginine methyl ester.[10] Although the role of this nuclear renin-angiotensin system remains mainly unknown, it may add to the diversity of the effects of AT_2R stimulation and hopefully help in better understanding its physiology.

Thus, reinterpretation of recently published articles using C21 in animal models of cardiovascular diseases is required. Nevertheless, it remains that C21 has beneficial effects against organ damage, although the precise mechanism of action is now less clear. Indeed, unlike C21, many commonly prescribed drugs are not well known, and their mechanism of action remains a matter of debate. Most importantly, much remains to be discovered concerning the role of AT_2R and the mechanisms involved in the cardiovascular system.

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Disclosures

None.

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