Hypertension Research (2014) 37, 614–615

www.nature.com/hr

COMMENTARY

The possible constitutive activity of wild-type angiotensin II type 1 receptor

Shin-ichiro Miura and Keijiro Saku

Hypertension Research (2014) **37,** 614–615; doi:10.1038/hr.2014.61; published online 13 March 2014

Wild-type (WT) G-protein coupled receptors (GPCRs), such as the α_{1B} adrenergic receptor, β_2 adrenergic receptor, 5-HT_1 receptor and angiotensin II (Ang II) type 2 (AT_2) receptor, display constitutive or spontaneous activities in the absence of an agonist.[1–3] In addition, several naturally occurring and disease-causing GPCR mutants with increased constitutive activity relative to WT GPCRs have been identified,[4] although no naturally occurring mutation in the AT_1 receptor can induce constitutive activity. If the Ang II type 1 (AT_1) WT receptor does have constitutive activity, we should be able to use this activity to classify many AT_1 receptor blockers (ARBs). Classifying clinically available ARBs as neutral agonists or inverse agonists should help to block the basal functionality of the AT_1 receptor.

It is unclear whether the constitutive activity of the AT_1 receptor could have a pathophysiological role or whether the blockade of this activity by an inverse agonist would help to prevent the progression of cardiovascular disease (CVD). To address this question, in this issue of *Hypertension Research*, Hasan *et al.*,[5] reported that inverse agonism of the AT_1 receptor attenuates spontaneous proinflammation and enhances the constitutive insulin-sensitizing activity of mature adipocytes. Inflammation and insulin-sensitizing activity contribute to the onset and progression of atherosclerotic CVD. High-dose valsartan reduced both the constitutive and Ang II-induced expression and secretion of interleukin-6 in mature adipocytes. The constitutive activity of the AT_1 receptor is thought to have a critical role in increasing inositol phosphate (IP) production.[6] Mechanical stress induces the constitutive activity of the AT_1 receptor and activates extracellular signal-regulated kinase, which contributes to cardiac remodeling.[7] However, losartan did not demonstrate inverse agonist activity toward IP production. The AT_1 receptor transgene in angiotensinogen-knockout mice showed cardiac enlargement, interstitial fibrosis and contractile dysfunction, which suggested that the transgenic myocardial overexpression of the AT_1 WT receptor increases the constitutive activity of the receptor, which leads to cardiac remodeling in the absence of Ang II.[7] Thus, inverse agonism of the AT_1 receptor may be important in preventing CVD progression. Apart from these reports, Hasan *et al.*,[5] were the first to indicate that the AT_1 WT receptor in adipocytes produced constitutive activity in adipocytokines. As obese rats exhibited marked upregulation of the AT_1 receptor mRNA and protein expression,[8] the pathological condition may be important. The authors proposed that the enhanced expression and secretion of adiponectin in mature adipocytes should also be a beneficial effect of valsartan in obese patients.

There is another important issue regarding the inverse agonism of ARB in mature adipocytes in Hasan's study.[5] Although valsartan and olmesartan have been shown to exhibit inverse agonism,[6,9] the authors did not analyze other ARBs. ARBs have been shown to demonstrate 'class' effects or 'common' effects. However, not all ARBs have the same effects, and some beneficial effects conferred by ARBs may be 'off-target' effects or 'molecular' effects rather than class effects.[10,11] We have proposed that the common molecular structures of ARBs might be responsible for their class effects, whereas their slightly different structures may be important for promoting molecule-specific effects.[10] Valsartan exhibits a strong inverse agonistic effect for IP production on AT_1 receptor.[6] However, valsartan is not an agonist for peroxisome proliferator-activated receptor (PPAR)-γ.[12] Other ARBs, such as telmisartan and irbesartan, have been shown to exhibit agonism for PPAR-γ as an off-target effect.[13,14] In addition, irbesartan inhibited monocyte chemoattractant protein-1 production from endothelial cells independent of the AT_1 receptor, and this effect may be mediated by nuclear factor kappa-B (NF-κB) inactivation.[14] The off-target effect of inverse agonism by inhibiting the constitutive activity of the AT_1 receptor by valsartan may also benefit anti-inflammation and enhance insulin-sensitizing activity. As mentioned above, valsartan did not directly stimulate PPAR-γ as an off-target effect. Interestingly, the inverse agonism of valsartan induced NF-κB inactivation and evoked cross-talk between NF-κB and PPAR-γ. PPAR coactivator-1α, which is essential for the transcriptional activity of PPAR-γ, was upregulated by valsartan. Thus, each ARB has critical and beneficial off-target effects. These effects may be caused by differences in the cell signaling mechanisms and in the types of cells.

Hasan's study has several limitations, which the authors noted.[5] The doses of Ang II and valsartan were fixed at relatively high levels. It is unclear whether a relatively high concentration of valsartan is clinically

S Miura and K Saku are at Department of Cardiology, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan; S Miura and K Saku are at Department of Molecular Cardiovascular Therapeutics, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan; S Miura is at Department of Molecular Cardiology, Cleveland Clinic Foundation, OH 44195, USA
E-mail: miuras@cis.fukuoka-u.ac.jp

relevant. The precise mechanisms underlying the constitutive activity of the AT_1 receptor inducing cell signaling in the NF-κB and PPAR-γ pathways are unclear. Further studies will be needed to clarify these points to ensure that we can clearly recognize the beneficial effects of the inverse agonism of valsartan.

In conclusion, Hasan's data clearly show that valsartan has beneficial off-target effects.[5] Although we can expect that other ARBs also have beneficial off-target effects, we must be careful when comparing their results and interpreting their clinical impacts. We should also reconsider whether ARBs have other beneficial off-target effects in addition to their class effects.

CONFLICT OF INTEREST

KS and SM have received grants and lecture honoraria from Daiichi-Sankyo, MSD, Dainippon Sumitomo Pharma, Takeda Pharma, Novartis Pharma, Boehringer Ingelheim and Astellas Pharma. KS is a Chief Director, and SM is a Director at NPO Clinical and Applied Science, Fukuoka, Japan. KS has an Endowed Department, 'Department of Molecular Cardiovascular Therapeutics' that is supported by MSD. SM belongs to the Department of Molecular Cardiovascular Therapeutics, which is supported by MSD.

ACKNOWLEDGEMENTS

KS and SM have received funding from Daiichi-Sankyo.

1 Costa T, Ogino Y, Munson PJ, Onaran HO, Rodbard D. Drug efficacy at guanine nucleotide-binding regulatory protein-linked receptors: thermodynamic interpretation of negative antagonism and of receptor activity in the absence of ligand. *Mol Pharmacol* 1992; **41**: 549–560.
2 Schutz W, Freissmuth M. Reverse intrinsic activity of antagonists on G protein-coupled receptors. *Trends Pharmacol Sci* 1992; **13**: 376–380.
3 Miura S, Karnik SS. Ligand-independent signals from angiotensin II type 2 receptor induce apoptosis. *EMBO J* 2000; **19**: 4026–4035.
4 Bais C, Santomasso B, Coso O, Arvanitakis L, Geras-Raaka E, Gutkind JS, Asch AS, Cesarman E, Gershengorn MC, Mesri EA, Gershengorn MC. G-protein coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. *Nature* 1998; **391**: 86–89.
5 Hasan AU, Ohmori K, Hashimoto T, Kamitori K, Yamaguchi F, Ishihara Y, Ishihara N, Noma T, Tokuda M, Kohno M. Valsartan ameliorates the constitutive adipokine expression pattern in mature adipocytes: a role for inverse agonism of the angiotensin II type 1 receptor in obesity. *Hypertens Res* 2014; **37**: 621–628.
6 Miura S, Kiya Y, Kanazawa T, Imaizumi S, Fujino M, Matsuo Y, Karnik SS, Saku K. Differential bonding interactions of inverse agonists of angiotensin II type 1 receptor in stabilizing the inactive state. *Mol Endocrinol* 2008; **22**: 139–146.
7 Yasuda N, Akazawa H, Ito K, Shimizu I, Kudo-Sakamoto Y, Yabumoto C, Yano M, Yamamoto R, Ozasa Y, Minamino T, Naito AT, Oka T, Shiojima I, Tamura K, Umemura S, Paradis P, Nemer M, Komuro I. Agonist-independent constitutive activity of angiotensin II receptor promotes cardiac remodeling in mice. *Hypertension* 2012; **59**: 627–633.
8 Xu ZG, Lanting L, Vaziri ND, Li Z, Sepassi L, Rodriguez-Iturbe B, Natarajan R. Upregulation of angiotensin II type 1 receptor, inflammatory mediators and enzymes of arachidonate metabolism in obese Zucker rat kidney: reversal by angiotensin II type 1 receptor blockade. *Circulation* 2005; **111**: 1962–1969.
9 Miura S, Fujino M, Hanzawa H, Kiya Y, Imaizumi S, Matsuo Y, Tomita S, Uehara Y, Karnik SS, Yanagisawa H, Koike H, Komuro I, Saku K. Molecular mechanism underlying inverse agonist of angiotensin II type 1 receptor. *J Biol Chem* 2006; **281**: 19288–19295.
10 Miura S, Karnik SS, Saku K. Review: angiotensin II type 1 receptor blockers: class effects versus molecular effects. *J Renin Angiotensin Aldosterone Syst* 2011; **12**: 1–7.
11 Imaizumi S, Miura S, Yahiro E, Uehara Y, Komuro I, Saku K. Class- and molecule-specific differential effects of angiotensin II type 1 receptor blockers. *Curr Pharm Des* 2013; **19**: 3002–3008.
12 Erbe DV, Gartrell K, Zhang YL, Suri V, Kirincich SJ, Will S, Perreault M, Wang S, Tobin JF. Molecular activation of PPARγ by angiotensin II type 1-receptor antagonists. *Vascul Pharmacol* 2006; **45**: 154–162.
13 Yamamoto K, Ohishi M, Ho C, Kurtz TW, Rakugi H. Telmisartan-induced inhibition of vascular cell proliferation beyond angiotensin receptor blockade and peroxisome proliferator-activated receptor-gamma activation. *Hypertension* 2009; **54**: 1353–1359.
14 Fujino M, Miura S, Kiya Y, Tominaga Y, Matsuo Y, Karnik SS, Saku K. A small difference in the molecular structure of angiotensin II receptor blockers induces AT_1 receptor-dependent and -independent beneficial effects. *Hypertens Res* 2010; **33**: 1044–1052.