Different Potencies of Angiotensin Receptor Blockers at Suppressing Adrenal β-Arrestin1-Dependent Post-Myocardial Infarction Hyperaldosteronism

Aldosterone is one of the various hormones with detrimental functions for the failing heart, whose circulating levels are elevated post-myocardial infarction (MI) and in patients with chronic heart failure (HF) (1). We have recently discovered that angiotensin II, acting through its type 1 receptors (AT₁Rs) in the adrenal cortex, can elicit aldosterone synthesis and secretion through both G protein- and β-arrestin (βarr1)-dependent signaling pathways, thereby exacerbating post-MI HF (1,2). In addition, the prototypic angiotensin receptor blocker (ARB) drug losartan appears to be ineffective at combating the adrenal βarr1-dependent hyperaldosteronism post-MI (2). Therefore, in the present study, we investigated the potencies of several other ARBs at suppression of adrenal βarr1-dependent post-MI hyperaldosteronism in vivo.

All methods have been described previously (2). One- or 2-way analysis of variance models with the Bonferroni test and/or Dunnett’s test, using SAS version 8.2 software (SAS Institute, Cary, North Carolina), were used for statistical comparisons.

Treatment for 7 days with valsartan or candesartan markedly reduced circulating aldosterone levels (post-MI-associated hyperaldosteronism) in post-MI rats overexpressing βarr1 specifically in their adrenal glands. However, irbesartan treatment for the same time period completely failed to do so (Figure 1A), which was similar to what has been found with losartan (2). This translated into significantly improved cardiac function in the post-MI animals treated with candesartan or valsartan, in terms of both ejection fraction (Figure 1B) and isoproterenol-stimulated contractility (Figure 1B), whereas irbesartan failed to halt the cardiac performance decline in these animals (Figure 1B). Additionally, candesartan significantly reduced post-MI cardiac fibrosis, whereas irbesartan once again had no effect (data not shown). Finally, the adverse remodeling-associated biomarkers collagen I, atrial natriuretic peptide, and B-type natriuretic peptide were significantly reduced by candesartan or valsartan, whereas irbesartan treatment failed to improve them (data not shown).

Significant differences in pharmacological and clinical properties exist among several ARBs currently on the market (3). Our present study adds another dimension to these differences: efficacy at adrenal βarr1-dependent post-MI hyperaldosteronism suppression. Our data suggest that candesartan and valsartan might be the most preferable members of this drug class to use in cardiovascular disease, especially if the condition is complicated by hyperaldosteronism. In contrast, irbesartan appears to be a weak inhibitor of βarr1-dependent hyperaldosteronism, which might underlie its lack of benefit in HF with preserved ejection fraction (3,4), although circulating aldosterone measurements were not reported in those clinical trials. However, candesartan, unlike irbesartan, seems to at least reduce hospitalizations in HF with preserved ejection fraction, and appears to be far superior to losartan for HF patients in terms of mortality lowering (3).

On the basis of our present study, the efficacy of each ARB at suppressing adrenal βarr1-dependent aldosterone production might play a role in the observed clinical differences between the ARBs. This obviously awaits confirmation from circulating aldosterone measurements in HF patients treated with these drugs.

Furthermore, the degree to which each ARB suppresses adrenal βarr1-dependent aldosterone also might underlie the “aldosterone breakthrough” phenomenon that often hampers the clinical use of ARB drugs (5). On the basis of our present findings, it is quite plausible that the adrenal βarr1-dependent aldosterone production pathway might be involved in this phenomenon. Thus, the stronger an ARB (e.g., candesartan, valsartan) is at inhibiting this pathway, the lower the risk of this side effect.

Candesartan and valsartan are the most efficacious post-MI hyperaldosteronism suppressors, whereas irbesartan and losartan are the least efficacious ARBs in that respect, probably due to different abilities at blocking adrenal AT₁₅R-activated βarr1. These pre-clinical findings strongly suggest that the
pharmacological effects of the ARB drugs on adrenal AT1R-activated βar1 have to be taken into account when comparing their clinical effectiveness in heart disease (e.g., HF) treatment or when their propensity for developing the “aldosterone breakthrough” phenomenon is considered.

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REFERENCES

Is 3-Dimensional Echocardiographic Area Strain Diagnostically Superior to Longitudinal and Circumferential Strain?

I read with interest and benefit the paper by Smith et al. (1) detailing 3-dimensional (3D) echocardiographic strain evaluation of the right ventricle for