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RESEARCH HIGHLIGHT

Which ARB drug is better for heart failure therapy? Aldosterone suppression holds the answer

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The known physiological effect of angiotensin II (AngII) type I receptors (AT_1Rs), synthesis and secretion of the cardiotoxic hormone aldosterone, whose elevation accompanies and aggravates heart failure (HF), is mediated by both G proteins and βarrestins (βarrs). We recently examined the relative potencies of all the currently used in the clinic AT_1R antagonist drugs (angiotensin receptor blockers, ARBs, or sartans) at preventing activation of either of these two signaling mediators at the AngII-bound AT_1R and, consequently, at suppression of aldosterone in vitro and in vivo. We also tested the impact of the aldosterone suppression they produce in vivo on the cardiac function of post-myocardial infarction (MI) animals progressing to HF. By using a variety of techniques in cultured cells in vitro, we found that all ARBs are potent inhibitors of G protein activation at the AT_1R but display striking differences in their potency at blocking the second signaling component of aldosterone production in the adrenal cortex, i.e. βarrs. Candesartan and valsartan in particular were found the most potent at blocking AngII-induced βarr activation at this receptor, translating into excellent efficacies at aldosterone suppression in vitro and in vivo and at post-MI cardiac function and remodeling amelioration. Conversely, irbesartan appears to be largely G protein- inhibitory, as it exhibits very low potency towards βarr inhibition. As a result, it is a very weak aldosterone suppressor in vitro and in vivo, and fails to improve cardiac function or adverse remodeling post-MI. These findings will aid pharmacotherapeutic decisions for therapy of post-MI HF and they will also help develop novel and better ARB drugs, with greater efficacy for HF therapy.

Keywords: Angiotensin Receptor Blockers; Aldosterone; Angiotensin II type 1 Receptor; beta-arrestin; heart failure

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Aldosterone is one of the various hormones with detrimental functions for the failing heart, whose circulating levels are elevated post-MI and in chronic HF [1]. It is produced and secreted by the adrenal cortex in response to AngII acting through its AT_1Rs, which are endogenously expressed in adrenocortical zona glomerulosa (AZG) cells [2]. AT_1R is a G protein-coupled receptor (GPCR) that also signals through G protein-independent pathways, a plethora of which are mediated by the scaffolding actions of βarrs, originally discovered as terminators of GPCR signaling [3]. We had previously reported that AngII elicits aldosterone synthesis and secretion via both G proteins and βarrs (specifically βarr1) (**Fig. 1**), which significantly exacerbates post-MI HF [4-6]. Of note, the prototypic drug of the ARB class losartan appears ineffective at blocking the adrenal βarr1-dependent aldosterone production and hence, at suppressing circulating aldosterone post-MI [5]. This phenomenon (i.e. failure at suppressing aldosterone) has been observed with several ARBs clinically and is sometimes referred to as "aldosterone breakthrough" [7-10]. Together,

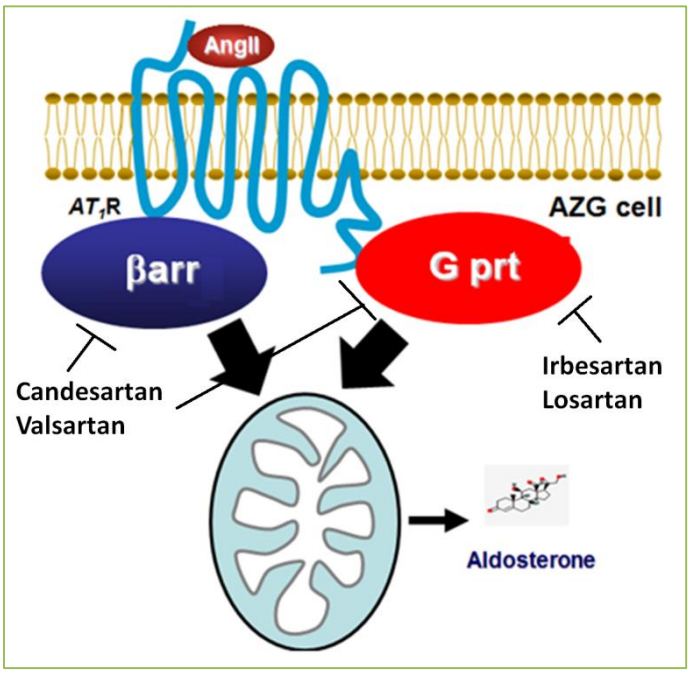

Figure 1. The two signaling components of AngII-activated AT_1R-induced aldosterone production. See text for details. AZG: Adrenocortical zona glomerulosa; βarr: βarrestin; G prt: G protein.

these findings prompted us to investigate the relative potencies of all ARBs at inhibiting these two signal transducers activated by the AT_1R and, consequently, gauge their efficacies at lowering aldosterone in vitro and in vivo.

By using two different but complementary cell-based assay systems, the proprietary DiscoveRx assay and the CellKey assay systems, we were able to verify that none of the marketed ARB drugs displays any agonist (or inverse agonist) activity for either G proteins or βarrs at the human AT_1R. In other words, none of them causes activation of either G proteins or βarrs intrinsically [11]. Next, we tested the relative potencies of the drugs at inhibiting βarrs vs. G proteins at the AngII-bound AT_1R and we were able to calculate their relative potencies for βarr and G protein inhibition in vitro. The drugs not belonging to the biphenyl-tetrazol derivatives subclass (azilsartan, telmisartan, and eprosartan) were all equipotent at blocking G proteins and βarrs, displaying "zero" selectivity in their AT_1R inhibition with respect to one signal transducer over the other. Among the tetrazolo-biphenyl-methyl derivatives however, losartan and irbesartan were extremely weak βarr inhibitors, being essentially G protein-specific inhibitors (**Fig. 1**) [11]. In contrast, valsartan and candesartan were extremely potent at blocking both βarrs and G proteins (**Fig. 1**) [11]. Next, we examined the impact of this on the physiological effect of AT_1R-induced aldosterone production in vitro. Using the human AZG cell line H295R, transfected to overexpress βarr1 [4], and in vitro aldosterone secretion as the readout, we found that candesartan and valsartan are by far the most potent aldosterone secretion inhibitors in vitro (**Fig. 1**) [11]. Olmesartan also displays some limited capability of suppressing secretion but losartan and irbesartan are completely incapable of suppressing SII-induced aldosterone secretion from these cells [11]. Consistent with these findings, candesartan and valsartan were also the most potent inhibitors of aldosterone synthesis, whereas losartan and irbesartan were completely incapable of reducing aldosterone synthesis in H295R cells [11].

Importantly, we were able to correlate these in vitro findings from the adreoncortical cells also in vivo, in post-MI rats progressing to HF and overexpressing βarr1 specifically in their adrenals [5]. More specifically, circulating plasma aldosterone levels, which are significantly elevated, due to the HF progression, in control vehicle-treated post-MI rats, were found markedly reduced at the end of a 7-day treatment regimen of either valsartan or candesartan, whereas irbesartan, similarly to what we had found previously with losartan [5], completely failed to reduce the post-MI-associated hyperaldosteronism of these animals, even after a whole week of treatment [12]. This translated into significantly improved cardiac function of the post-MI HF animals, in terms of both ejection fraction and isoproterenol (a standard cardiac positive inotrope)-stimulated contractility by valsartan or candesartan, whereas the failure of irbesartan to suppress circulating aldosterone levels translated into progressively worsening cardiac function in these animals [12]. Finally, the 7-day treatment with candesartan significantly reduced post-MI cardiac fibrosis in adrenal βarr1-overexpressing rats compared to control vehicle-treated animals, whereas irbesartan treatment for the same time period had no effect [11]. Additionally, the adverse remodeling-associated biomarkers collagen I, atrial natriuretic peptide, and B-type natriuretic peptide, which are markedly elevated by the hyperaldosteronism the adrenal βarr1 overexpression causes [5], were significantly reduced by candesartan after 1 week of treatment, compared to the control vehicle-treated animals and irbesartan treatment for the same time period failed, again, to reduce any of these markers [12]. Taken together, these results indicate that, consistent with their effects on cardiac function and contractility, candesartan significantly halts and/or reverses cardiac adverse remodeling post-MI, despite the presence of the adrenal βarr1-driven hyperaldosteronism, whereas irbesartan can improve neither cardiac function, nor adverse remodeling, in the face of adrenal βarr1-driven hyperaldosteronism.

These findings add a new dimension to the differential pharmacology and physiology of the ARB drug class [13,14]: these drugs differ also in their potencies at preventing βarr

activation by the AT_1R, which, in the adrenal cortex, translates into aldosterone production that, in turn, can exacerbate HF. 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 elevated aldosterone levels. In contrast, irbesartan appears to be a weak inhibitor of βarr1-dependent aldosterone turnover, which might underlie its lack of benefit in diastolic HF (HF with preserved ejection fraction, HF-PEF) [15,16]. On the other hand, candesartan seems to reduce hospitalizations in HF-PEF, a benefit that irbesartan lacks [16], and appears to be far superior over losartan for HF patients in terms of mortality lowering [14]. Thus, it is quite plausible that the efficacy of an ARB drug at blocking βarrs at the AngII-activated AT_1R and, consequently, at suppressing circulating aldosterone levels determines the observed clinical differences between the individual agents in the class. Of course, the confirmation of this theory can only come from measurements of circulating aldosterone levels in HF patients treated with these drugs.

In addition, the degree to which each ARB prevents βarr activation by the AngII-bound adrenocortical AT_1R might underlie the "aldosterone breakthrough" phenomenon that often hampers the clinical use of these agents [8-10]. Given that all ARBs appear more or less equally potent at blocking the G protein-dependent component of the AT_1R signaling towards aldosterone production in the AZG cells, but display significant differences in their potencies at blocking the βarr component, it is quite plausible that the adrenal βarr-dependent aldosterone production pathway is responsible for the manifestation of the "aldosterone breakthrough" phenomenon upon ARB use, and, the stronger inhibitor of this pathway an ARB drug is, the lower the risk of this side-effect. Based on our present study, and if this hypothesis holds true, candesartan and valsartan appear to be the ARBs with the lowest risk for "aldosterone breakthrough" but, obviously, further studies are needed to address this question and confirm this hypothesis.

Finally, from the medicinal chemistry point of view, a substitution both bulky and negatively charged on the biphenyl-tetrazolo-backbone (as in candesartan and valsartan) appears to confer strong βarr inhibition at the AT_1R; losartan and irbesartan have bulky but unionized R_1 substitutions (and are weak βarr inhibitors). Based on this observation, we have designed and are currently investigating the compound: 2-pentyl-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1*H*-1,3-benzodiazole-7-carboxylic acid, which satisfies both of these structural criteria, and our preliminary data indicate that it is a very potent aldosterone suppressor and βarr inhibitor at the adrenocortical AT_1R (A. Lymperopoulos, data unpublished).

In conclusion, by comparing all the ARBs currently on the market head-to-head, candesartan and valsartan appear the most potent βarr antagonists at the AT_1R, in contrast to irbesartan and losartan, which are mainly G protein-selective antagonists, with very low potency at βarr inhibition. These findings translate into candesartan and valsartan having the best efficacy at suppressing aldosterone secretion in vitro and circulating aldosterone post-MI in vivo, whereas irbesartan and losartan display the worst efficacy at doing so. Consistent with their effects on circulating aldosterone in vivo, candesartan and valsartan are also the most efficacious ARBs at improving post-MI cardiac function/remodeling, whereas irbesartan fails to halt HF progression in post-MI rats. Future studies in post-MI patients treated with these drugs, as well as further preclinical studies in post-MI animals with long-term ARB drug treatments, are needed to confirm these findings and help incorporate them into clinical practice.

Conflicting interests

The authors declare no competing financial or any other interests or any relationship with the industry.

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