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Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy

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Abstract

Aldosterone mediates many of the physiological and pathophysiological/cardio-toxic effects of angiotensin II (AngII). Its synthesis and secretion from the zona glomerulosa cells of the adrenal cortex, elevated in chronic heart failure (HF), is induced by AngII type 1 receptors (AT₁Rs). The AT₁R is a G protein-coupled receptor, mainly coupling to G_{q/11} proteins. However, it can also signal through β-arrestin-1 (βarr1) or -2 (βarr2), both of which mediate G protein-independent signaling. Over the past decade, a second, G_{q/11} protein-independent but βarr1-dependent signaling pathway emanating from the adrenocortical AT₁R and leading to aldosterone production has become appreciated. Thus, it became apparent that AT₁R antagonists that block both pathways equally well are warranted for fully effective aldosterone suppression in HF. This spurred the comparison of all of the currently marketed angiotensin receptor blockers (ARBs, AT₁R antagonists or sartans) at blocking activation of the two signaling modes (G protein-, and βarr1-dependent) at the AngII-activated AT₁R and hence, at suppression of aldosterone *in vitro* and *in vivo*. Although all agents are very potent inhibitors of G protein activation at the AT₁R, candesartan and valsartan were uncovered to be the most potent ARBs at blocking βarr activation by AngII and at suppressing aldosterone *in vitro* and *in vivo* in post-myocardial infarction HF animals. In contrast, irbesartan and losartan are virtually G protein-“biased” blockers at the human AT₁R, with very low efficacy for βarr inhibition and aldosterone suppression. Therefore, candesartan and valsartan (and other, structurally similar compounds) may be the most preferred ARB agents for HF pharmacotherapy, as well as for treatment of other conditions characterized by elevated aldosterone.

Key words: Adrenal cortex; Adrenocortical zona glomerulosa cell; Aldosterone; Angiotensin receptor blocker; Angiotensin II type 1 receptor; β-arrestin-1; Heart failure;

Suppression efficacy

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Core tip: The angiotensin II type 1 receptor (AT₁R) endogenously expressed in adrenocortical cells was known for decades to induce aldosterone production *via* a well-defined G_q protein-mediated signaling pathway. Over the past decade, a number of studies have elucidated another, β -arrestin-1 (β arr1)-dependent signaling cascade, which proceeds in parallel to, and independently of the G_q-mediated one, and also results in aldosterone synthesis and secretion from the adrenal cortex. Importantly, although all of the Food and Drug Administration-approved angiotensin receptor blocker (ARB) drugs (AT₁R antagonists) are very effective at blocking the G_q-mediated pathway, as expected, since they were designed to do so (*i.e.*, to block the G protein signaling of the AT₁R), they seem to display varying efficacies at blocking this new, β arr1-dependent pathway, which translates into significant variation at aldosterone suppression efficacies. In that context, candesartan and valsartan appear the most effective agents at blocking also the β arr1 pathway emanating from the adrenocortical AT₁R, and thus, these two agents may be the best aldosterone suppressors within the ARB drug class.

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INTRODUCTION

Aldosterone is a mineralocorticoid hormone with several cardio-toxic actions, whose plasma levels are extremely high in chronic heart failure (HF) negatively affecting progression of the disease^[1]. Amongst its main actions on the failing myocardium is overall promotion of adverse remodeling *via* maladaptive hypertrophy, chamber dilatation, collagen deposition and fibrosis, increased inflammation and reactive oxygen species production, *etc.* The net result of all of these effects is acceleration of cardiac functional decline^[2-4]. The main source of circulating aldosterone is the adrenocortical zona glomerulosa (AZG) cells, which synthesize and secrete it in response to high serum K⁺ levels (hyperkalemia), since its main action on the kidneys is K⁺ excretion (along with Na⁺ and water reabsorption)^[5]. Another powerful physiological stimulus for aldosterone secretion from AZG cells is the octapeptide hormone angiotensin II (AngII), which activates its type 1 receptors (AT₁Rs), endogenously expressed in AZG cells^[5,6].

The AT₁R is a 7-transmembrane-spanning or G pro-

tein-coupled receptor (GPCR); upon agonist activation, it couples primarily to the G_{q/11} family of G proteins^[6]. Nowadays however, it is known to signal also through other types of G proteins, like G_{i/o} and G_s, as well as through G protein-independent pathways mediated by the universal GPCR adapter proteins β -arrestin-1 (β arr1) and β arr2 (also known as arrestin-2 and -3, respectively)^[7-9]. The β arrs bind agonist-activated and GPCR-kinase (GRK)-phosphorylated GPCRs to uncouple them from G proteins (receptor desensitization) and to target them to clathrin-coated vesicles for internalization (receptor endocytosis). At the same time, they initiate their own, "second wave" of signal transduction independently of G proteins^[10-13].

ANGII-DEPENDENT ALDOSTERONE PRODUCTION: THE SUM OF TWO SIGNALING MODALITIES

The G_{q/11} protein-dependent signaling pathway elicited by the AngII-activated AT₁R that culminates in aldosterone synthesis and secretion in AZG cells has been well characterized (Figure 1)^[14]. More specifically, diacylglycerol (DAG) and inositol trisphosphate (IP₃), the two second messengers produced by this pathway, ultimately lead to: (1) aldosterone secretion, *via* elevated intracellular free Ca²⁺ concentration, which directly stimulates exocytosis and hormonal (in the context of AZG cells, aldosterone) secretion; and (2) aldosterone synthesis, *via* extracellular signal-regulated kinase (ERK) MAPK activation, which, in turn, stimulate aldosterone biosynthesis in AZG cells by transcriptionally upregulating the StAR (steroidogenic acute regulatory) protein^[14]. This protein mediates the mitochondrial uptake of the precursor of all adrenal steroids cholesterol and is the rate-limiting enzyme of aldosterone biosynthesis in AZG cells^[14].

In the chronic HF setting, adrenal GRK2 is up-regulated and, along with β arr1, hyperphosphorylates and severely desensitizes the sympatho-inhibitory α_2 -adrenergic receptors (ARs) of chromaffin cells in the adrenal medulla^[15-21]. The result of this is chronic elevation of adrenal catecholamine secretion, which significantly contributes to the heightened sympathetic nervous system outflow and increased norepinephrine and epinephrine levels that further damage the failing heart^[22-26]. Since aldosterone is also increased in HF and its production is stimulated by the AT₁Rs of the adrenal cortex^[1], which are also GRK2 and β arr1 substrates, it was theorized that the upregulated (in HF) adrenal GRK2 could lead to excessive interaction of β arr1 also with the AT₁R in the adrenal cortex, thereby modulating aldosterone secretion in the chronic HF setting, as well. Indeed, this was found to be the case^[27]. *Via* a combination of *in vitro* experiments in the human AZG cell line H295R and *in vivo* experiments in experimental rats developing HF following an acute, surgically induced myocardial infarction (MI), we were

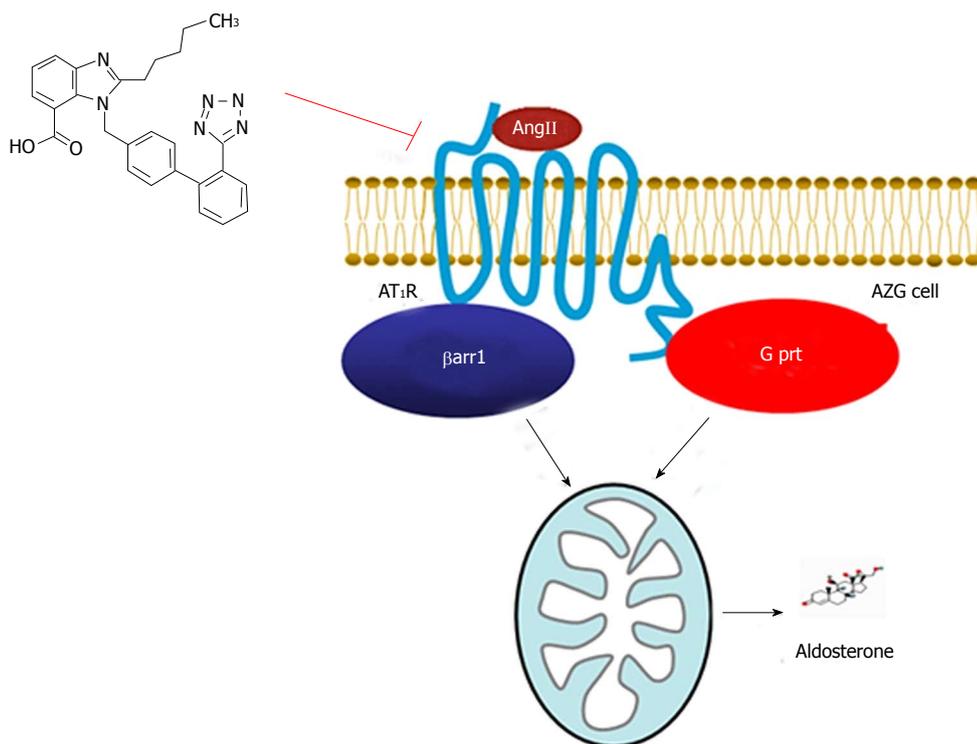


Figure 1 Angiotensin II type 1 receptor and aldosterone production. Schematic representation of the parallel G prt- and β arr1-mediated, AngII-bound AT1R signaling cascades that converge on mitochondrial aldosterone synthesis in adrenocortical zona glomerulosa (AZG) cells. The structure of the proposed AT1R antagonist (2-pentyl-1-((4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl)methyl)-1H-1,3-benzodiazole-7-carboxylic acid)^[40], discussed in the text, capable of suppressing both pathways equally well, is also shown (upper left corner). See text for details. G prt: Gq protein; β arr1: β -arrestin1; AngII: Angiotensin II; AT1R: AngII type 1 receptor.

able to show that adrenal β arr1 actually promotes AngII-dependent aldosterone synthesis and secretion by also mediating AT₁R signaling to ERK-dependent StAR upregulation independently of G proteins (Figure 1)^[27,28]. This finding was somewhat surprising, given that β arr1 would normally be expected to reduce AngII-dependent aldosterone production thanks to desensitizing the AT₁R (terminating its G protein-dependent signaling, see above). Nevertheless, it was discovered that, after abolishing the G_q-dependent signaling by the AT₁R in AZG cells, AT₁R-bound β arr1 initiated its own signaling to aldosterone synthesis by recruiting a DAG-kinase to the activated receptor^[29], which converted the second messenger lipid DAG to phosphatidic acid (PA)^[27]. PA can directly activate the small (monomeric) G protein Ras at the plasma membrane, which then initiates the cascade that results in ERK phosphorylation and activation^[30]. Thus, AT₁R-activated β arr1 elicits a “second (delayed) wave” of signaling leading to sustained ERK activation in AZG cells in its own right (*i.e.*, independently of G proteins), which, as discussed above, promotes aldosterone production *via* StAR upregulation^[27]. Importantly, since StAR regulates synthesis not only of aldosterone but of all adrenal steroids throughout the three anatomical zones of the adrenal cortex^[14], adrenal β arr1 may also affect the synthesis of glucocorticoids and of androgens in the adrenal cortex.

Notably, adrenal β arr1 may not only stimulate the

AT₁R-dependent aldosterone synthesis *via* its “second wave” of signaling to ERK-dependent StAR upregulation but also facilitate the acute AT₁R-dependent aldosterone secretion at the plasma membrane of AZG cells and in parallel to the G protein-mediated signaling by the receptor (Figure 1). Recent evidence in transfected heterologous systems suggests such a role in the “first wave” of GPCR signaling for the β arrs^[31,32] and a very intriguing study, done specifically in the adrenal medulla, suggested an acute stimulation of catecholamine secretion and of Ca²⁺-dependent exocytosis by AT₁R-activated β arr1 (but interestingly not by β arr2) in adrenal chromaffin cells, thanks to its direct interaction with the plasma membrane Ca²⁺ channel short transient receptor potential channel-3 (TRPC3)^[33]. Thus, it is quite plausible that AT₁R-bound β arr1 can directly stimulate TRPC3-dependent Ca²⁺ currents and hence, exocytosis, also in AZG cells, thereby acutely stimulating AngII-dependent aldosterone secretion within seconds of agonist binding (and in parallel to the G_q-mediated signaling by the AT₁R). This interesting possibility of another signaling mechanism by which β arr1 can induce aldosterone production in AZG cells is definitely worthy of investigation in future studies.

Most importantly, adrenal β arr1-dependent aldosterone production has been documented to occur also *in vivo*, both under physiological (in normal, healthy animals) and pathophysiological (in the post-MI HF setting) conditions^[27,28]. Specifically, adrenal-targeted

β arr1 overexpression increased aldosterone serum levels *in vivo* in normal rats^[27], and caused severe hyperaldosteronism also in post-MI rats on top of the circulating aldosterone elevation normally occurring due to the MI injury^[28]. Importantly, in the latter animals, adrenal-specific β arr1 blockade *in vivo* with a β arr1 C-terminal fragment during post-MI HF progression helped stall the decline of cardiac function and even reversed several aspects/markers of adverse cardiac remodeling courtesy of normalization of circulating aldosterone levels^[28]. What's more, aldosterone levels remarkably show no increase in β arr1-knockout mice post-MI, which further highlights the importance of adrenal β arr1 in regulation of circulating aldosterone levels^[34]. Together, these *in vivo* studies strongly suggest adrenal β arr1, in conjunction with GRK2, as an attractive therapeutic target for diseases associated with, and aggravated by hyperaldosteronism, such as post-MI HF^[9,25]. Adding to its importance as a therapeutic target is also the fact that aldosterone can produce effects independently of its mineralocorticoid receptor (MR) (the so-called "non-genomic" actions of aldosterone)^[4]. Obviously, these effects cannot be countered by MR antagonist drugs (*e.g.*, eplerenone, finerenone, spironolactone) and thus, suppression of aldosterone production at its source, *i.e.*, the adrenal cortex, *via* adrenal β arr1 blockade would be much more preferable from the therapeutic standpoint.

WHICH ARB DRUG WINS THE ALDOSTERONE SUPPRESSION "CONTEST"?

The realization that AngII-dependent aldosterone production from the adrenal cortex proceeds through two independent signaling modalities, *i.e.*, G α protein- and β arr1-dependent (Figure 1), signaled that complete blockade of both of these modalities is needed to attain full suppression of adrenal aldosterone production and effectively lower circulating aldosterone levels in HF and in other diseases. This, coupled with the fact that some AT $_1$ R antagonist drugs (angiotensin receptor blockers, ARBs, or sartans) appear ineffective at lowering aldosterone in HF, despite their full capacity to block AT $_1$ R-G protein coupling^[35-38], prompted us to test the relative efficacy of the currently available ARBs at inhibiting the β arr1-dependent aldosterone production by the AT $_1$ R in an effort to identify the most effective agent(s). Indeed, the prototypic agent of this class, losartan, was found totally ineffective at preventing adrenal β arr1-dependent aldosterone production and combatting hyperaldosteronism post-MI due to very weak antagonism of β arr1 activation by the AT $_1$ R^[28]. Interestingly however, the active metabolite of losartan EXP1374 was found quite effective at blocking AT $_1$ R-dependent aldosterone production and β arr1 activation^[39,40].

Upon subsequent head-to-head testing of all the

currently Food and Drug Administration (FDA)-approved ARB drugs, it was found that, although all ARBs (including losartan) are potent inhibitors of G protein activation by the AT $_1$ R, their potencies at preventing β arr1 activation by the human AT $_1$ R *in vitro* varied enormously^[40]. Specifically, candesartan and valsartan appeared the most potent blockers of β arr1 activation and the most efficacious aldosterone suppressors *in vitro* and *in vivo*^[39,40]. At the opposite end of the spectrum and in addition to losartan, was irbesartan, which was found to be a very weak β arr1 inhibitor and hence, a very ineffective aldosterone suppressor both *in vitro* and *in vivo*, despite its excellent G protein-blocking ability^[39,40]. The rest of the class fell more or less in the middle of the β arr1 inhibition and AT $_1$ R-dependent aldosterone suppression scales, *i.e.*, their potency values were lower than candesartan's and valsartan's but much higher than losartan's and irbesartan's^[39,40]. Importantly, their effects on cardiac function of in post-MI HF animals *in vivo* were in complete concordance with their effects on circulating aldosterone levels; candesartan and valsartan induced significant improvements in cardiac function and remodeling post-MI, whereas irbesartan and losartan were not able to alter the course of progression of post-MI animals to full-blown HF^[39].

IMPLICATIONS FOR HF PHARMACOTHERAPY

It is widely recognized nowadays that the members of the ARB drug class display significant variation in their pharmacological and clinical properties, which has significant repercussion for their use in HF pharmacotherapy^[41]. In fact, certain agents have already been shown to afford larger improvements in morbidity and mortality of chronic HF than others^[42-45]. Part of the reason for these differences among these agents that belong to the same pharmacological class and share the same mechanism of action (AT $_1$ R antagonism) may be differences in their efficacies at combating the hyperaldosteronism that accompanies and burdens chronic HF^[1]. In other words, agents that suppress aldosterone effectively are bound to work better for HF therapy and, since adrenal β arr1 plays a pivotal role in regulation of this cardio-toxic hormone's levels, the ARBs that are most effective at blocking the AT $_1$ R- β arr1 interaction in the adrenal cortex would be expected to be preferred agents. In that vein, our aforementioned recent findings that candesartan and valsartan are the most efficacious β arr1 inhibitors at the AT $_1$ R, coupled with their excellent efficacy at lowering aldosterone *in vitro* and *in vivo*, point to these two ARBs as being the most preferable agents of their class to use in HF treatment (and in other hyperaldosteronic conditions, *e.g.*, salt-sensitive hypertension). In contrast, irbesartan and losartan were found very weak β arr1-dependent aldosterone inhibitors, a finding that may have some bearing on the lack of therapeutic benefit of these two

agents demonstrated in HF with preserved ejection fraction (HF-PEF) and on their therapeutic inferiority to candesartan in terms of HF mortality reduction^[44,45]. Of course, future trials providing data on the serum aldosterone levels of the ARB-treated HF patients are needed to confirm such a link between adrenal β arr1-dependent aldosterone suppression efficacy and clinical benefit for this important cardiovascular drug class.

On the other hand, failure of these agents to suppress aldosterone, otherwise referred to as "aldosterone breakthrough" or "aldosterone escape", is a clinically well-documented phenomenon^[46-49] and the efficacy of each agent at inhibiting β arr1-dependent aldosterone production may be inversely proportional to the probability of the ARB to exhibit it. In other words, the more potent β arr1-dependent aldosterone suppressor an ARB is, the lower the likelihood is that the treated patient will suffer from "aldosterone breakthrough". Thus, candesartan and valsartan may be the safest ARB drugs to use in HF patients in terms of the risk of "aldosterone breakthrough". However, large trials closely monitoring the circulating aldosterone levels of treated patients are again needed in order to confirm this hypothesis.

IMPLICATIONS FOR AT₁R BLOCKER MEDICINAL CHEMISTRY

The studies on the relative potencies/efficacies of the currently FDA-approved ARBs at inhibiting AT₁R- β arr1 interaction and β arr1-dependent aldosterone turnover provided some interesting medicinal chemistry and pharmacological insights, as well. Specifically, as far as the ARBs that are tetrazolo-biphenyl-methyl derivatives are concerned, which is a subgroup that includes losartan (and its metabolite EXP1374), irbesartan, candesartan, valsartan, and olmesartan, it was concluded that a substitution both bulky and negatively charged attached to the one side of the methylene group of the biphenyl-methyl backbone (the other end has the tetrazolo-biphenyl group attached) is needed to confer good inhibitory potency of β arr1 at the AT₁R and consequently, effectively suppress aldosterone^[40]. Indeed, both candesartan and valsartan, as well as EXP1374, have spacious, long aliphatic chain-containing and anionic (carboxylic acid) groups attached to that end of the biphenyl-methyl backbone^[40]. In contrast, both losartan and irbesartan possess neutrally charged (unionizable) groups (albeit also bulky) at that biphenyl-methyl backbone end^[40]. Finally, olmesartan, which also has an anionic (carboxylic acid) substitution but of intermediate bulkiness (*i.e.*, less long aliphatic chain) compared to candesartan and valsartan on that side of its backbone, displays intermediate potency at inhibiting β arr1 activation and suppressing aldosterone^[40]. Based on these observations, we have designed the compound 2-pentyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-1,3-benzodiazole-7-carboxylic acid (Figure 1)^[40], which carries a bulky,

carboxyl acid group with a long aliphatic chain on the other end of the tetrazolo-biphenyl-methylene backbone, and we are currently testing both its potency at blocking β arr1 activation by the human AT₁R and its efficacy at suppressing aldosterone secretion *in vitro* and in the post-MI HF setting *in vivo*. Our hope is that it will prove to be even more efficacious than candesartan and valsartan at suppressing aldosterone levels and thus, an even better drug for HF treatment than all currently available ARBs. Of course, the above mentioned ARB structure-activity relationship inferences have to be confirmed by crystal structure resolutions of the AT₁R bound to β arrs. The first glimpse into the human AT₁R crystal structure was recently provided and it was the first step towards that goal^[50]. Unfortunately however, that crystal structure lacked the intracellular C-terminal tail of the receptor, which is exactly the AT₁R region that interacts with β arrs^[51].

CONCLUSION

A head-to-head comparison of the ARBs currently on the United States market identified candesartan and valsartan as the most potent β arr1 antagonists and the most efficacious aldosterone suppressors at the human AT₁R. Conversely, irbesartan and losartan were found to be largely G protein-"biased" inhibitors, with minimal efficacy towards inhibition of AngII-dependent aldosterone production. Thus, from a therapeutic standpoint, candesartan and valsartan may be the most preferable agents of this drug class, as they provide the biggest benefit for cardiac function and patient survival in post-MI HF and have the lowest propensity to cause the "aldosterone escape" adverse effect (failure to suppress aldosterone). Future studies on this class of drugs and on the effects of β arrs at the adrenal AT₁R will help solidify these inferences and will also provide additional important information regarding AngII/AT₁R pharmacology for clinicians and medicinal chemists alike.

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