Regulation of aldosterone in heart failure and vascular aging: implications for therapy

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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 2,3 etc. (Fig. 1). The net result of all of these effects is acceleration of cardiac functional decline 4-6. 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) 7.

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 7,8. The AT1R is a 7-transmembrane-spanning or G protein-coupled receptor (GPCR); upon agonist activation, it couples primarily to the Gq/11 family of G proteins 8. Nowadays however, it is known to signal also through barrestin-1 (barr1) or -2 (barr2), both of which mediate G protein-independent signaling. Over the past decade, a second, Gq/11 protein-independent but barr1-dependent signaling pathway emanating from the adrenocortical AT1R and leading to aldosterone production has come to the light, signifying that AT1R antagonists that block both G proteins and barrs at the AT1R equally well are needed to achieve full suppression of aldosterone. Indeed, although all marketed angiotensin receptor blockers (ARBs, AT1R antagonists or sartans) potently inhibit G protein activation, candesartan and valsartan were found to be the most potent agents at blocking also barr activation. Therefore, these two drugs are portended to be the most effective aldosterone suppressors in vitro and in vivo in post-myocardial infarction (MI) HF animals. Finally, in addition to HF, hypertension, and other cardiovascular diseases, aldosterone is implicated also in arterial aging and associated vascular fibrosis, making it a potential therapeutic target for cardiovascular disease treatment in geriatric patients.

Key words: Adrenocortical zona glomerulosa cell, Aldosterone, Angiotensin II type 1 Receptor, Barrestin-1, Heart Failure, Vascular aging
internalization (receptor endocytosis). At the same time, they initiate their own, “second wave” of signal transduction independently of G proteins 12-15.

**A NEW PLAYER IN AT1R SIGNALING TO ALDOSTERONE PRODUCTION: BARR1**

The Gq/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 16. More specifically, diacylglycerol (DAG) and inositol trisphosphate (IP3), the two second messengers produced by the Gq-activated phospholipase C (PLC)β, ultimately lead to: a) aldosterone secretion, via elevated intracellular free Ca2+ concentration, which directly stimulates exocytosis and hormonal (in the context of AZG cells, aldosterone) secretion, and b) aldosterone synthesis, via extracellular signal-regulated kinase (ERK) MAPK activation, which, in turn, stimulates aldosterone biosynthesis in AZG cells by transcriptionally upregulating the steroidogenic Acute Regulatory (StAR) protein (Fig. 1) 16. 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 16. In the chronic HF setting, adrenal GRK2 is upregulated and, along with barr1, hyperphosphorylates and severely desensitizes the sympatho-inhibitory a2-adrenergic receptors (ARs) of chromaffin cells in the adrenal medulla 17-23. 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 24-29. 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 barr1 substrates, it was theorized that the upregulated (in HF) adrenal GRK2 could lead to excessive interaction of barr1 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 30. 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 able to show that adrenal barr1 actually promotes AngII-dependent aldosterone synthesis and secretion by also mediating AT1R signaling to ERK-dependent StAR upregulation independently of G proteins (Fig. 1) 30-31. This finding was somewhat surprising, given that barr1 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 Gq-dependent signaling by the AT1R in AZG cells, AT1R-bound barr1 initiated its own signaling to aldosterone synthesis by recruiting a DAG-kinase (DGK) to the activated receptor 32, which converted the second messenger lipid DAG to phosphatidic acid (PA) 30. 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 33. Thus, AT1R-activated barr1 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 30. Importantly, since STAR regulates synthesis not only of aldosterone but also of all adrenal steroids throughout the three anatomical zones of the adrenal cortex 16, adrenal barr1 may also affect the synthesis of glucocorticoids and of androgens in the adrenal cortex.

Notably, adrenal barr1 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 (Fig. 1). Recent evidence in transfected heterologous systems suggests such a role in the “first wave” of GPCR signaling for the barrs 34-35 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 barr1 (but interestingly not by barr2) in adrenal chromaffin cells, thanks to its direct interaction with the plasma membrane Ca2+ channel TRPC3 (short transient receptor potential channel-3) 36. Thus, it is quite plausible that AT1R-bound barr1 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 Gq-mediated signaling by the AT1R). This interesting possibility of another signaling mechanism by which barr1 can induce aldosterone production in AZG cells is definitely worthy of investigation in future studies.

Most importantly, adrenal barr1-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 30-31. Specifically, adrenal-targeted barr1 overexpression increased aldosterone serum levels in vivo in normal rats 30, and caused severe hyperaldosteronism also in post-MI rats on top of the circulating aldosterone elevation normally occurring due to the MI.
Importantly, in the latter animals, adrenal-specific barr1 blockade in vivo with a barr1 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. What's more, aldosterone levels remarkably show no increase in barr1-knockout mice post-MI, which further highlights the importance of adrenal barr1 in regulation of circulating aldosterone levels. Together, these in vivo studies strongly suggest adrenal barr1, in conjunction with GRK2, as an attractive therapeutic target for diseases associated with, and aggravated by hyperaldosteronism, such as post-MI HF. 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). 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 barr1 blockade would be much more preferable from the therapeutic standpoint. Implications for the ARB drug class & HF pharmacotherapy

The involvement of barr1 in AngII-dependent aldosterone production from the adrenal cortex, coupled with the fact that some ARBs appear ineffective at lowering aldosterone in HF, despite their full capacity to block AT1R-G protein coupling 38-41, prompted investigation of the relative efficacies of the currently available ARBs at suppressing barr1-dependent aldosterone production. The prototypic agent of this class, losartan, was found ineffective at preventing adrenal barr1-dependent aldosterone production and combatting hyperaldosteronism post-MI due to very weak antagonism of barr1 activation by the AT1R 31 42. Interestingly however, the active metabolite of losartan EXP1374 was found quite effective at blocking AT1R-dependent aldosterone production and barr1 activation 43 44. Conversely, candesartan and valsartan were the most potent blockers of barr1 activation and the most efficacious aldosterone suppressors in vitro and in vivo 44 45. At the opposite end of the spectrum, together with losartan, was irbesartan, which was found to be a very weak barr1 inhibitor and hence, a very ineffective aldosterone suppressor both in vitro and in vivo, despite its excellent G protein-blocking ability 44 45. Importantly, effects on cardiac function of post-MI HF animals in vivo were in complete concordance with effects on circulating aldosterone levels, i.e. candesartan and valsartan induced significant improvements in cardiac function and remodeling, whereas irbesartan and losartan were not able to halt HF progression 44.

Given the significant variation in pharmacological and clinical properties, such as improvements in morbidity and mortality of chronic HF, of the ARBs 45-49, it is quite plausible that their differences in aldosterone-suppressing efficacy may underlie at least some of these pharmacological and clinical differences. In other words, the ARBs that are most effective at blocking the AT1R-barr1-dependent aldosterone production may afford the biggest improvement in HF morbidity and mortality. Indeed, candesartan and valsartan, which are the most efficacious barr1-mediated aldosterone suppressors (see above), have been reported to improve HF patient survival to a larger extent than losartan 46- 51. In contrast, irbesartan, which was found to be very weak at blocking barr1-dependent aldosterone, shows no benefit in HF with preserved ejection fraction (HF-PEF) and appears inferior to candesartan in terms of HF mortality reduction 48 49. 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 barr1-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 barr1-dependent aldosterone production may be inversely proportional to the probability of the ARB to exhibit it.

**IMPLICATIONS FOR AGING**

In addition to the heart, aldosterone promotes hypertrophy, fibrosis, inflammation, and oxidative stress also in arteries (Fig. 1) 54-56. This aldosterone-dependent vascular fibrosis can be quenched by mineralocorticoid receptor blockers, such as spironolactone, eplerenone and finerenone 57. Interestingly, in aging, aldosterone levels appear to decline rather than increase 58 59, but vascular mineralocorticoid receptors, which mediate most of the effects of aldosterone, are upregulated in aged intact vessels and in vascular smooth muscle cells isolated from aged animals, correlating with increased vascular fibrosis 60. Nevertheless, more studies are needed to delineate the precise role of mineralocorticoid receptor signaling in aging-related vascular fibrosis and to validate aldosterone as a therapeutic target for geriatric heart disease.

**CONCLUSIONS & FUTURE PERSPECTIVES**

It is now well appreciated that AngII-dependent aldosterone production is a complicated process involving not only G protein signaling but also barr-dependent (G protein-independent) signal transduction. Recent studies have identified candesartan and valsartan as the most potent barr signaling antagonists, hence the most efficacious aldosterone suppressors in vitro and in vivo. Thus, from a therapeutic standpoint, candesartan and valsartan may be the most preferable agents of the ARB drug class, at least for post-MI HF treatment. On the other hand, the role of aldosterone in vascular fibrosis and hypertension, albeit well established during adulthood, is still under intense investigation in the context of aging. Future studies on aldosterone antagonists and ARBs in animal models of aging and, of course, in geriatric patients will help elucidate the therapeutic potential of targeting this hormone for geriatric cardiovascular therapy.
References


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