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Review

Mineralocorticoid receptors in vascular function and disease

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ABSTRACT

The mineralocorticoid receptor (MR), a member of the steroid receptor family, regulates blood pressure by mediating the effects of the hormone aldosterone (Aldo) on renal sodium handling. Over the past decade, it has become clear that MR is expressed in the cardiovascular system and interest has grown in understanding the direct role of the MR in regulating vascular function and contributing to cardiovascular disease. This interest stems from multiple clinical studies in which drugs that decrease MR activation also reduce the incidence of heart attacks, strokes, and mortality out of proportion to modest changes in systemic blood pressure. The presence of functional mineralocorticoid receptors in vascular smooth muscle and endothelial cells is now well established and, while still controversial, data supports the vasculature as an Aldo-responsive tissue. This review summarizes recent advances in our understanding of the role of vascular MR in regulating normal vascular function and in promoting vascular disease. *In vitro* data, *in vivo* animal studies, and human data are reviewed suggesting a role for MR-activation in promoting vascular oxidative stress, inhibiting vascular relaxation, and contributing to vessel inflammation, fibrosis, and remodeling. These detrimental vascular effects of MR activation appear to be independent of changes in blood pressure and are synergistic with the presence of endothelial dysfunction or damage. Thus, in humans with underlying cardiovascular disease or cardiovascular risk factors, vascular MR activation may promote vascular aging and atherosclerosis thereby contributing to the pathophysiology of heart attack, stroke, and possibly even hypertension. Further exploration of the molecular mechanisms for the detrimental vascular effects of MR activation has the potential to identify novel therapeutic targets to prevent or treat common cardiovascular disorders.

Contents

Abbreviations: 11βHSD2, 11-beta-hydroxysteroid dehydrogenase type 2; Aldo, aldosterone; Ang2, angiotensin 2; AT1R, angiotensin type1 receptor; BP, blood pressure; CETP, cholesterol–ester-transfer-protein; CTGF, connective tissue growth factor; EC, endothelial cells; ECM, extracellular matrix; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; GC, guanylyl cyclase; HDL, high density lipoprotein; ICAM1, intercellular adhesion molecule 1; IGF, insulin-like growth factor; MCP-1, monocyte chemoattractant protein; MR, mineralocorticoid receptor; NO, nitric oxide; NOS, nitric oxide synthase; PAI-1, plasminogen activator inhibitor 1; PDGF, platelet derived growth factor; PGF, placental growth factor; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells.

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1. Introduction: A role for mineralocorticoid receptors in clinical vascular outcomes

The mineralocorticoid receptor (MR), a member of the steroid receptor family, was identified 25 years ago as a critical regulator of blood pressure (BP) by mediating the effects of the hormone aldosterone (Aldo) on renal sodium handling (Rogerson and Fuller, 2000; Arriza et al., 1987). It has since become clear that MR is expressed in non-epithelial cells and interest has grown in understanding the direct role of MR in regulating vascular function and in contributing to cardiovascular diseases. This interest stems from multiple clinical studies demonstrating that inhibition of the renin–angiotensin–aldosterone system (RAAS) prevents vascular ischemic events (heart attacks and strokes) and cardiovascular mortality in diverse patient populations (The SOLVD Investigators, 1991, 1992; Dagenais et al., 2001; Dahlof et al., 2002; Pitt et al., 1999, 2003; Zannad et al., 2011). These benefits were initially attributed to the BP-lowering and potential cardiac remodeling effects of RAAS antagonism with secondary vascular consequences. However, the vascular benefits of MR antagonism in these clinical trials are significantly greater than that expected from the modest decrease in systemic BP with inconsistent effects on cardiac remodeling (Udelson et al., 2010), supporting a direct role for vascular MR-activation in vascular pathology. Additional studies directly support that RAAS antagonists have BP-independent effects on vascular remodeling and cardiovascular events (Dahlof et al., 2002; Lonn et al., 2001). Although the physiologic ligand for vascular MR is still controversial and will be discussed in this review, the importance of understanding the direct vascular effects of Aldo-activated vascular MR has been recently highlighted by clinical data supporting that autonomous Aldo elevation may contribute to a larger fraction of essential hypertension than previously appreciated (Gonzaga and Calhoun, 2008) and by the failure in clinical trials of the HDL-raising CETP-inhibitor torcetrapib, likely due to an off target rise in serum Aldo. In the torcetrapib trials, despite significant improvements in cholesterol profiles (Nissen et al., 2007; Bots et al., 2007; Barter et al., 2007), post hoc analyses support that electrolyte and serum evidence of even mild Aldo excess correlated with increased carotid intimal thickness, coronary atherosclerosis, cardiovascular ischemic events, and mortality in patients with underlying cardiovascular risk factors (Nicholls et al., 2008; Vergeer et al., 2008; Duriez, 2007).

Many studies from the 1970s to the 1990s explored the effects of Aldo on the vasculature and this work has been reviewed previously (Rocha and Funder, 2002). This review specifically focuses on advances in the past decade in our understanding of the role of MR in directly regulating vascular function and in promoting vascular disease. MR activation may alter vascular function via genomic mechanisms, in which MR functions as a ligand-activated transcription factor to modulate vascular gene expression, and by non-genomic, rapid effects of MR that intersect with multiple important vascular signaling pathways including those of epidermal growth factor (EGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), and angiotensin 2 (Ang2). A complete discussion of the non-genomic actions of Aldo and MR is beyond the scope of this review and is summarized elsewhere in this issue. In each section of this review, the most recent data regarding the role of MR will be summarized first in vascular cells *in vitro*, followed by *in vivo* studies in animal models, and finally in human subjects.

2. MR expression and function in the vasculature

The blood vessel is a layered structure with an inner intima, composed of a single layer of endothelial cells (EC) that line the lumen and contact circulating blood, a medial layer, composed of vascular smooth muscle cells (VSMC), and an outer adventitial layer, containing fibroblasts and extracellular matrix (ECM, see model in Fig. 2, top). In the late 1980s and early 1990s, studies demonstrated Aldo binding and MR expression in vascular cells and in whole vessels from animals and humans (reviewed in Lombes et al., 2000). More recently, it has been confirmed that endogenous MR in human vascular cells and vessels can directly respond to ligand to regulate vascular-specific gene expression programs that can modulate vascular cell functions involved in cardiovascular pathophysiology (Jaffe and Mendelsohn, 2005; Jaffe et al., 2007, 2010; Caprio et al., 2008; Newfell et al., 2011).

Two endogenous ligands, Aldo and cortisol, bind to human MR with equal affinity (Arriza et al., 1987). Although plasma glucocorticoid concentrations are higher than those of Aldo, Aldo-responsive tissues, such as the kidney, maintain Aldo responsiveness by expressing the cortisol-inactivating enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11βHSD2, (Funder et al., 1988)). Although still debated, the expression and function of 11βHSD2 in VSMC and EC has now been demonstrated in multiple studies from many groups supporting the idea that the vasculature is an Aldo-responsive tissue (Kornel, 1994; Brem et al., 1998; Alzamora et al., 2000; Hatakeyama et al., 2000; Kayes-Wandover and White, 2000; Christy et al., 2003; Jaffe and Mendelsohn, 2005; Caprio et al., 2008). Indeed clinical studies demonstrate that even modest increases in serum Aldo levels, as in patients with heart failure, hypertension, or those treated with torcetrapib, produce BP-independent alterations in vascular function lending support for a role for Aldo in directly regulating vascular function *in vivo* in humans (Farquharson and Struthers, 2000; Gonzaga and Calhoun, 2008; Nissen et al., 2007; Bots et al., 2007; Barter et al., 2007; Nicholls et al., 2008; Vergeer et al., 2008; Duriez, 2007). However, the possibility still exists that under specific conditions or in specific subsets of vascular cells, cortisol could activate vascular MR. For example, in a subset of cultured aortic SMC prone to calcification, 11βHSD2 expression and function are decreased compared to unselected aortic SMC (Jaffe et al., 2007). Whether subsets of vascular cells respond to cortisol *in vivo* is not known, and if cortisol does act as a vascular MR–ligand under specific conditions, the differential vascular effects of Aldo- versus cortisol-bound MR remain to be explored. In addition, as with other steroid receptors, MR can be activated by ligand-independent mechanisms. MR-mediated gene transcription in human vascular cells has been shown to be activated by direct action of Ang2 (and other factors in serum) via hormone-independent mechanisms that remain to be clarified (Caprio et al., 2008; Jaffe and Mendelsohn, 2005).

Aldo is produced in the zona glomerulosa of the adrenal gland. Extra-adrenal synthesis of Aldo in tissues including the heart has also been reported (Silvestre et al., 1998; Slight et al., 1999). Expression of Aldo synthase (CYP11B2) and production of Aldo, was originally reported in vascular cells and vessels (Hatakeyama et al., 1994; Takeda et al., 1995a,b, 1996; Kayes-Wandover and White, 2000), however, subsequent studies have failed to demonstrate Aldo biosynthesis in the vasculature (Ahmad et al., 2004; Gomez-Sanchez et al., 2004; Jaffe and Mendelsohn, 2005) and the physiological relevance of vascular Aldo production remains controversial. Regardless of the Aldo source, it is now generally accepted that vascular cells contain functional MR capable of responding directly to Aldo through genomic and non-genomic mechanisms to regulate normal vascular function and contribute to cardiovascular disease.

3. MR, aldosterone, and vascular oxidative stress

The production of reactive oxygen species (ROS) by the vasculature, termed vascular oxidative stress, is a critical determinant of vascular function and a significant contributor to vascular