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Review

Cardiac effects of aldosterone: Does gender matter?

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ABSTRACT

Ischemic heart disease (IHD) continues to be the most common cause of death globally, although mortality rates are decreasing with significant advances in treatment. Higher prevalence of co-morbidities in women only partly explains the lack of decrease in mortality rates in younger women due to. Until recently there has been gender bias in pre-clinical studies and many clinical trials, resulting in a significant gap in knowledge whether there are differential responses to therapy for women, particularly younger women. There is increasing evidence that there are significant gender-specific differences in the outcome of post-infarction remodelling, prevalence of hypertension and sudden cardiac death. These differences indicate that cardiac tissue in females displays significant physiological and biochemical differences compared to males. However, the mechanisms mediating these differences, and how they change with age, are poorly understood. Circulating levels and physiological effects of aldosterone vary across the menstrual cycle suggesting female steroid sex hormones may not only regulate production of, but also responses to, aldosterone in pre-menopausal women. This modified tissue response may foster a homeostatic environment where higher levels of aldosterone are tolerated without adverse cardiac effect. Moreover, there is limited data on the direct regulation of this signalling axis by androgens in female animals/subjects. This review explores the relationship between gender and the effects of aldosterone in cardiovascular disease (CVD), an issue of significant need that may lead to changes in best practice to optimise clinical care and improve outcomes for females with CVD.

Contents

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death globally and a public health burden given the aging population. Men have earlier onset and more severe ischemic heart dis-

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ease (IHD) than premenopausal women however the primary cause of death for women after myocardial infarction (MI) is IHD. Whereas mortality rates in men are decreasing due to advances in treatment strategies, mortality rates in women 35–54 years old have not changed, or increased [1,2], with annual mortality rates greater than breast cancer [3]. This is partly due to younger women having a higher prevalence of comorbidities at presentation; however, even when these factors are considered, younger women continue to have greater risk of early mortality [4].

Activation of the renin–angiotensin–aldosterone system (RAAS) contributes to many of the complications of CVD and hence using angiotensin receptors (AII-R) blockers, angiotensin-converting enzyme inhibitors (ACEI) and mineralocorticoid receptor (MR) antagonists are effective treatment strategies, although sex-specific differences in efficacy of treatment are not routinely determined. Sex differences have been reported in cardiac remodelling during aortic stenosis and hypertension [5], with women having increased left ventricular wall thickness and concentric hypertrophy [6], although mechanisms have not been defined. Interestingly, sex-specific cardiac remodelling in women who did not have myocardial infarction and heart failure in the Framingham Heart Study, correlated with increased serum levels of aldosterone [7]. Further, more women (49%) than men (19%) with primary aldosteronism carry the KCNJ5 mutation [8], which may facilitate membrane depolarization and development of aldosterone producing adenoma. The focus of this review is on the cardiac effects of aldosterone, the final mediator in RAAS and to review the available evidence whether there are sex differences that need to be considered for further investigation to optimise treatment strategies.

2. Genomic and non-genomic actions

It is 60 years since aldosterone was isolated and characterised [9] as the primary regulator of salt and water homeostasis in the kidney and colon. Since then, a multitude of other actions have been identified in target organs as diverse as the brain [10], vasculature [11], adipose tissue [12], retina [13] and the focus of this review, the heart [14–16]. Similar to other steroid hormones, aldosterone has both genomic and non-genomic actions. The biological actions of aldosterone involve binding to its cognate receptor, the mineralocorticoid receptor (MR), which is the second member of group 3C in the nuclear receptor superfamily (NR3C2). Similar to other steroid hormones, aldosterone has both genomic and non-genomic actions. Genomic regulation by aldosterone is mediated when ligated MR interacts with protein co-regulators; the hormone–receptor complex then translocates to the nucleus and modulates transcription of various target genes [17]. The rapid extranuclear, non-genomic effects of aldosterone are not dependent on transcription and protein synthesis [18–21] and mediated through MR-dependent and MR-independent mechanisms [22–26], some of which are mediated via the G protein-coupled receptor 30 (GPR-30 or GPER) [27,28].

3. Circulating levels of aldosterone

Adverse cardiac effects of elevated plasma levels of aldosterone, in combination with high-salt intake include hypertrophy [29,30], inflammation and fibrosis [14,15,31,32], left ventricular remodelling post-MI [33,34], apoptosis [16] and heart failure [35]. Even in the absence of heart failure or acute MI, patients with coronary artery disease who had elevated levels of aldosterone were at increased risk of acute ischaemic events and death [36]. The hypokalemia and hypomagnesaemia accompanying elevated plasma levels of aldosterone, increases the risk of sudden cardiac death (SCD) [37]. We have previously shown that elevated serum levels of aldosterone also raise the levels of intracellular sodium [38] by inhibiting the most significant sodium efflux mechanism in the heart, Na^+–K^+ pump activity. Inhibition of pump activity may also contribute to cardiac remodelling by activating key growth-related genes in cardiac myocytes [39]. However, these experimental studies were conducted in male animals and the clinical studies had few women enrolled (<30%) [34–36].

Previous reports of plasma levels of aldosterone in pre-menopausal women provide variable results, with elevated levels compared to men reported in the Framingham Offspring Study [40], decreased levels [41] or regulated by phases of the human menstrual cycle, with elevated levels during luteal phase [42–44]. Discrepancy between these studies may result from failure to account for differences in dietary sodium (Na^+) intake, a major regulator of aldosterone production [45], position of the subjects at the time of blood collection, time of day and medications. Several of these studies used radioimmunoassay (RIA) to measure the concentration of aldosterone in plasma, which may have also contributed to these variable results, due to cross-reactivity with structurally related compounds [46] and therefore has low specificity. Increasing use of high sensitivity and specificity high performance liquid chromatography (HPLC) in combination with tandem mass spectrometry (LC–MS/MS) [44,47–48] may provide more reliable measures, since aldosterone concentrations measured by LC–MS/MS are lower when compared to RIA [47].

Elevated circulating levels of aldosterone do not always translate to a physiological response, with reduced peripheral vascular resistance and no change in blood pressure reported with enhanced aldosterone levels [49], suggesting additional mechanisms are involved. Since levels of progesterone and estrogen also increase during the luteal phase of the menstrual cycle [43], we suggest further studies in pre-menopausal women are required to consider the possible influence of these steroids in regulating the cardiac action of aldosterone. There are suggestions that increased aldosterone production is secondary to increased progesterone [42,44], competing with aldosterone for MR [50–52]. When sodium balance is controlled, there is no change in plasma Ang II or renin, suggesting RAS-independent stimulation of aldosterone production during the luteal phase [43]. Progesterone added to isolated rat zona glomerulosa cells resulted in 2.8-fold increase in aldosterone production, whereas estradiol had no effect [43] and hence further studies are required to identify the relationship between aldosterone and progesterone. Plasma levels of progesterone are reported as ~200 pg/ml in men, whereas in women, levels were ~500 pg/ml and ~9000 pg/ml during follicular and midluteal phases, respectively [53]. However, circulating progesterone is tightly bound to plasma proteins and hence free progesterone is only 1–3% of plasma levels [54], with differential effects reported for the class of progestins indicating the effects are not the same across this class of mediators [55]. Therefore, the crosstalk between progestins and aldosterone need to be considered for prospective studies into the cardiac actions of aldosterone in pre-menopausal women.

4. Sex hormones and cardiac actions of aldosterone

Experimental studies provide variable reports of the role of sex steroids during myocardial infarction (MI). Ovariectomy aggravates cardiac remodelling post-MI [56], whereas there is either no difference in infarct size or cardiac remodelling between males and females [57] or reduced infarct size post-MI for females [58]. We have recently identified key roles for sex steroids during MI, to regulate the balance between autophagy and apoptosis (Fig. 1), with less cardiac damage in females due to reduced apop-