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Role of Mineralocorticoid Receptors in Arterial Stiffness in Human Aging

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Abstract

Arterial stiffness, an independent predictor of cardiovascular disease, is increased in aging, but the underlying mechanisms are not completely understood. Mineralocorticoid receptors (MR) may contribute to oxidative stress and arterial stiffness in healthy older adults. To test the hypothesis that short-term MR blockade may reduce oxidative stress and improve arterial stiffness, we conducted a randomized, double blind, crossover study using the selective MR blocker Eplerenone or placebo in 23 older adults (age, 64±1 years; mean±SE) free from overt cardiovascular and other clinical disease (e.g, diabetes, renal and liver disease). In response to MR blockade, brachial and carotid blood pressure decreased (P≤0.01). However, MR blockade had no effect on oxidative stress (oxidized LDL, 61.2±6.8 vs. 62.4±7.4 U/L, P=0.9; placebo vs. Eplerenone) and arterial stiffness (aortic pulse wave velocity (PWV), 9.17±1.19 vs. 8.92±1.19 m/sec, P=0.5; leg PWV, 13.45±0.45 vs. 12.81±0.47 m/sec, P=0.3; arm PWV, 11.43±0.62 vs. 11.73±0.68 m/sec, P=0.7; carotid artery compliance, 0.150±0.013 vs. 0.149±0.014 mm^2/mmHg, P=0.8; distensibility, 23.1±1.8 vs. 23.3±1.7 10^{-3}/kPa, P=0.8; β stiffness index, 3.5±0.3 vs. 3.6±0.3, P=0.6; and augmentation index, 16.0±2.2 vs. 15.6±2.8 %, P=0.8). These results provide the first evidence that MR do not appear to contribute to oxidative stress in human aging and that short-term MR blockade does not result in reduced oxidative stress and improved arterial stiffness.

Keywords

aging; oxidative stress; arterial stiffness; compliance; augmentation index; pulse wave velocity

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1. Introduction

Aging is associated with stiffening of the large central elastic arteries, and increased wave reflection (Mitchell, 2008). Large elastic artery stiffness is a strong predictor of future cardiovascular events and all-cause mortality in older adults (Meaume et al., 2001; Sutton-Tyrrell et al., 2005), thus understanding the mechanisms contributing to age-related arterial stiffness is important.

A key determinant of arterial stiffness is vascular smooth muscle cell tone. Oxidative stress and nitric oxide acutely modulate vascular smooth muscle cell tone and arterial stiffness (Kinlay et al., 2001; Mullan et al., 2002). In mice, short-term nitrite supplementation has been found to decrease oxidative stress, improve nitric oxide bioavailability and reverse age-related large elastic artery stiffness (Sindler et al., 2011). In patients with type 2 diabetes, four weeks of daily oral antioxidant (i.e., ascorbic acid) administration has been shown to improve arterial stiffness (Mullan et al., 2002). Interestingly, acute reduction in oxidative stress resulting from ascorbic acid infusion, has also been found to increase large elastic artery compliance in healthy older postmenopausal women (Moreau et al., 2005). These findings suggest that elevated oxidative stress is an important mechanism contributing to arterial stiffness.

With aging, arterial superoxide levels increase, partly due to excessive activity of NADPH oxidase, leading to inactivation of nitric oxide (Adler et al., 2003) and arterial stiffness (Sindler et al., 2011). There is considerable evidence that mineralocorticoid receptors (MR) activate NADPH oxidase-dependent superoxide production and contribute to decreased nitric oxide levels (Keidar et al., 2004; Rajagopalan et al., 2002). Moreover, MR blockade has been shown to decrease NADPH oxidase activity, reduce superoxide formation, and improve nitric oxide bioavailability (Sartorio et al., 2007). These observations led us to postulate that in aging, increases in arterial stiffness might be mediated by MR-related oxidative stress, but to our knowledge, this has not been previously investigated.

Thus, in the current study, we hypothesized that short-term MR blockade would reduce oxidative stress and improve arterial stiffness and wave reflection in human aging. To test this hypothesis we administered in a randomized, double blind, placebo-controlled, crossover study the selective MR antagonist Eplerenone and measured oxidative stress, arterial stiffness and wave reflection with and without MR blockade in older adults free of clinical disease.

2. Methods

2.1 Subjects

Twenty-three adults (10 men and 13 women), 55 to 79 years of age were enrolled in this study. All subjects were sedentary, non-smokers and were free of overt cardiovascular and other clinical diseases (e.g., diabetes, liver and renal disease) as assessed by medical history, physical examination, resting ECG, urinalysis, blood chemistries and hematological evaluation. All subjects demonstrated normal ECG and blood pressure responses to a graded exercise test on a treadmill. The exercise testing protocol has previously been described (Christou et al., 2005). Briefly, after a 6-10 minute warm-up, subjects walked at a comfortable speed that corresponded to 70 to 80% of their age-predicted maximal heart rate. The treadmill grade was increased 2.5% every two minutes until volitional exhaustion. Three subjects had resting systolic blood pressure between 140 and 143 mmHg, whereas one subject had elevated resting systolic and diastolic blood pressure (148/96 mmHg). None of the subjects was taking antihypertensive or vasoactive medications. Women were postmenopausal and were not on hormone replacement therapy for at least 2 years prior to

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data collection. This study was carried out in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Boards of the University of Florida, Texas A&M University, and Scott & White Health System. The purpose, nature, and risks of the study were explained to the volunteers and their written informed consent was obtained prior to participation.

2.2 Study design

We used a randomized, double blind, placebo-controlled, crossover experimental design. A daily dose of 100 mg Eplerenone (MR antagonist) or placebo (Consolidated Midland Corporation, Brewster, New York) was administered for 1 month, with 1-month washout between treatments. Experimental measures were obtained at the end of each treatment.

Eplerenone was chosen for this study for the following reasons: 1) Eplerenone has been designed to selectively bind to MR unlike Spironolactone, which is a non-specific antagonist of MR, progesterone and androgen receptors; and 2) Eplerenone does not have the adverse side effects (e.g., gynecomastia in men, breast tenderness and menstrual problems in women) which are associated with Spironolactone (Jeunemaitre et al., 1988). Although, *in vitro*, Eplerenone has lower affinity for MR compared to Spironolactone, *in vivo*, a 50% lower dose of Eplerenone compared to Spironolactone is required to inhibit aldosterone binding to MR (de Gasparo et al., 1987). We chose a dose of 100 mg per day because doses larger than100 mg do not confer a greater effect.

To reduce the risk of hyperkalemia, subjects were not enrolled in the study if their baseline serum potassium was greater than 5.5 mmol/L, serum creatinine was greater than 1.6 mg/dL or creatinine clearance was less than 30 mL/min. In addition, to monitor subject safety during participation in the study, serum potassium and blood pressure were also assessed at baseline, day 3, day 7 and weekly thereafter for each treatment. No subjects were withdrawn from the study because of elevated serum potassium levels or low systolic blood pressure in response to the 1-month treatment. Participant compliance during the study was ~ 97% as assessed by the number of pills returned at the end of each treatment.

2.3 General experimental procedures

All measurements were performed in a semi-darkened temperature-controlled room after a minimum of 15 minutes of supine quiet rest. Subjects abstained from caffeine and completed a 12-hour overnight fast prior to data collection. To characterize the different components of arterial stiffness, we measured carotid arterial compliance and distensibility, β stiffness index, augmentation index (AIx), aortic, leg and arm pulse wave velocity (PWV).

2.4 Carotid artery compliance and blood pressure

Resting blood pressure was measured over the brachial artery with a semi-automated device (Dinamap, GE, Salt Lake City, UT, USA). Carotid arterial compliance was measured using high-resolution ultrasonography (Toshiba Aplio XV) and simultaneous applanation tonometry (TCB-500 Millar Instruments) as previously described (Tanaka et al., 2000). Briefly, the common carotid artery was imaged with the ultrasound transducer placed at a 90° angle to the vessel so that the near and far walls were clearly visualized. Diameters were measured at ~2 cm proximal to the carotid bulb using a commercially available wall tracking software package (Vascular Analysis Tools 5.8.2, Medical Imaging Applications, LLC, Iowa City, IA, USA). Systolic (maximal) and diastolic (minimal) carotid diameters were identified based on carotid pressure waveform. The carotid pressure waveform and amplitude were obtained with a pencil-type transducer with a pressure sensor at the tip. To assess carotid blood pressure, the tonometry signal was calibrated using the brachial blood pressure (diastolic and mean arterial pressure) to account for hold down pressure

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(Armentano et al., 1995). Carotid arterial compliance, a measure of arterial buffering capacity (O'Rourke et al., 2002) was calculated as: $[(D1-D0)/D0]/[2(P1-P0)]\pi(D0)^2$, where D1 and D0 are the maximal and minimal carotid diameters and P1 and P0 are the highest and lowest carotid blood pressures. The β stiffness index, a measure of arterial compliance adjusted for distending pressure (Hirai et al., 1989), was calculated as: (logP1/P0)/[(D1-D0)/D0]. Carotid arterial distensibility, a measure of arterial elastic properties (Reneman et al., 2005), was calculated as: [2(D1-D0)/D0]/(P1-P0).

2.5 Pulse wave analysis

AIx, a measure of the load placed on the left ventricle due to the amplitude and timing of the wave reflection, was determined using the applanation tonometry waveform as previously described (Christou et al., 2005). Briefly, AIx was calculated as the ratio of augmented pressure (i.e., amplitude of the carotid pressure wave above its systolic shoulder or inflection point) to the total carotid pulse pressure.

2.6 Pulse wave velocity

PWV, considered to be the gold standard measure of arterial stiffness in humans, was determined as previously described (Christou et al., 2005). Two transcutaneous Doppler flowmeters (model 810-A, Parks Medical) were used to simultaneously acquire blood flow velocity pulse waves from two recording sites. Pulse waves were recorded at the aortic arch (suprasternal notch) and femoral artery for aortic PWV, at the femoral artery and posterior tibial artery adjacent to the medial malleolus for leg PWV and at the brachial and radial artery for arm PWV. Aortic PWV represents central large elastic artery stiffness, whereas leg and arm PWV represent peripheral muscular artery stiffness. Pulse waves were digitized and analyzed with the signal-processing software WINDAQ (Dataq Instruments). PWV was calculated from the time delay between the foot of the two pulse waves and the distance between the proximal and distal recording sites. The foot was defined as the point at which the sharp systolic upstroke originated.

2.7 Oxidative stress

Plasma oxidized low density lipoprotein, an indirect measure of oxidative stress, was measured using a commercially available ELISA kit (Mercodia).

2.8 Height, weight, and adiposity measures

Height was measured to the nearest mm using a stadiometer. Body weight was measured to the nearest 0.1 kg with an electronic scale (Tanita, Arlington Heights, IL, USA) while subjects were barefoot and dressed in light clothing. Body mass index (BMI) was determined as weight divided by height squared (kg/m^2). Total body fat % was assessed with dual-energy x-ray absorptiometry (DPX-IQ, GE/Lunar, Salt Lake City, UT, USA) (Christou et al., 2005).

2.9 Statistics

Statistical analyses were performed using SPSS (version 20). Paired t-tests were used to compare arterial stiffness with and without MR blockade. Statistical significance for all analyses was set at $P< 0.05$. Data are reported as mean±SE.

3. RESULTS

Study participants ranged in age from 55 to 79 years (mean±SE: 64±1 years). Mean values and ranges for the main subject characteristics are presented in Table 1.

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MR blockade reduced brachial blood pressure (systolic: 127±3 vs. 120±2 mmHg, P=0.001; diastolic: 74±1 vs. 72±1 mmHg, P=0.02; pulse pressure: 53±2 vs. 48±2 mmHg, P=0.004; placebo vs. Eplerenone) and carotid blood pressure (systolic: 112±3 vs. 106±1 mmHg, P=0.002 and pulse pressure: 39±2 vs. 34±2 mmHg, P=0.006). Systolic and diastolic carotid diameters also decreased slightly (8.0±0.2 vs. 7.9±0.2 mm, P=0.01 and 7.6±0.2 vs. 7.5±0.2 mm, P=0.02, respectively). MR blockade had no effect on oxidized LDL (61.2±6.8 vs. 62.4±7.4 U/L, P=0.9), carotid compliance, distensibility, β stiffness index, AIx or aortic, arm and leg PWV (Table 2; P≥0.3).

4. DISCUSSION

This randomized, double blind, placebo-controlled, crossover study found that short-term blockade of MR does not lead to reduced oxidative stress, or improved arterial stiffness and wave reflection in older adults free from cardiovascular and other clinical disease despite reductions in peripheral and central blood pressures. To our knowledge, the present investigation is the first to examine the contribution of MR to oxidative stress and arterial stiffness in older adults free from overt clinical disease.

It is well known that MR activation by aldosterone regulates blood pressure by modulating renal sodium reabsorption and body fluid volume. Over the past decade, there has been increasing evidence of functional extra-adrenal MR, including presence in vascular endothelial (Nguyen Dinh Cat et al., 2010) and smooth muscle cells (McCurley et al., 2012). MR are now recognized to play a role in modulating oxidative stress, vascular tone, vascular function and cardiovascular pathophysiology (Keidar et al., 2004; McCurley and Jaffe, 2012; McCurley et al., 2012; Nguyen Dinh Cat et al., 2010; Rajagopalan et al., 2002). In our study, we found that daily oral administration of 100 mg of the selective MR blocker Eplerenone significantly reduces brachial and carotid blood pressure without affecting oxidative stress or arterial stiffness in healthy aging. In agreement with our results, McCurley et al. recently demonstrated in mice, that smooth muscle cell MR directly modulate blood pressure in aging without affecting arterial stiffness(McCurley et al., 2012). We are not aware of other studies in animals or humans examining the role of MR on arterial stiffness in healthy aging. In patients with isolated hypertension, ACE inhibition has also been found to lower blood pressure without improving arterial stiffness (Mackenzie et al., 2009). The blood pressure lowering effects of MR blockade in our study are possibly due to a reduction in plasma volume. This cannot be confirmed because we did not measure plasma volume, however, plasma volume has previously been shown to decrease with MR blockade (Rossignol et al., 2011).

Arterial stiffness has previously been shown to improve in response to acute antioxidant infusions (Moreau et al., 2005) or other short-term interventions (i.e., lasting a few weeks) (Mullan et al., 2002). Gates et al. have demonstrated in healthy older adults that arterial compliance increases by the end of the first week of dietary sodium restriction and peaks by the second week of the intervention (Gates et al., 2004). In addition, 3 weeks of angiotensin receptor blockade has been shown to improve arterial stiffness in patients with metabolic syndrome (Nashar et al., 2004) and 4-week oral administration of ascorbic acid has been found to improve arterial stiffness in type 2 diabetes (Mullan et al., 2002). We postulated that in healthy aging, MR blockade-related reductions in oxidative stress would lead to improved arterial stiffness by influencing vascular smooth muscle tone, but our findings did not support our expectations. The current investigation was designed with the goal of evaluating short-term MR-related effects, instead of vascular wall composition changes that require long-term interventions. We recognize that the length of our intervention does not allow us to rule out that long-term treatment with Eplerenone could lead to changes in

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vascular structure, and in turn, improved arterial stiffness in healthy aging. However, this was not the focus of the current investigation.

Our study is limited by the relatively small sample size. However, according to power calculations based on the negligible MR blockade-related changes in arterial stiffness in this study (0.6 to 2.6%), an unrealistic sample size (between 806 to 5358 subjects) would be required to demonstrate a statistically significant change in arterial stiffness. Such minor changes in arterial stiffness, even if statistically significant, would most likely not be physiologically/clinically important. Finally, we recognize that because our subjects were free from overt clinical disease, our results are restricted to healthy older adults.

5. CONCLUSIONS

Arterial stiffness predicts risk for future cardiovascular events (myocardial infarction, stroke, aortic syndromes), total cardiovascular mortality and all-cause mortality (Vlachopoulos et al., 2010). Thus, there is a strong need for understanding the underlying molecular mechanisms and for developing new therapies to prevent or reverse it. Our results demonstrate that short-term MR blockade in older adults free from overt clinical disease does not decrease oxidative stress nor lead to improved arterial stiffness and wave reflections. These findings suggest that MR do not tonically contribute to oxidative stress in human aging because blocking MR does not affect oxidative stress levels.

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Highlights

- Arterial stiffness (AS) is increased in aging but the underlying mechanisms are unclear.
- Mineralocorticoid receptors (MR) may contribute to oxidative stress and AS.
- We performed a randomized, double blind, crossover, MR blockade study in older adults.
- Oxidative stress and AS are not improved with MR blockade in healthy human aging.

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Table 1

Subject characteristics.

	Mean±SE	Min-Max
Weight, kg	88.7±4.2	54.8-132.7
Body mass index, kg/m^2	29.6±1.4	20.0-44.6
Body fat, %	39.6±1.8	25.6-54.1
Total cholesterol, mg/dL	185±7	119-246
LDL cholesterol, mg/dL	113±6	56-177
HDL cholesterol, mg/dL	49±2	31-74
Triglycerides, mg/dL	115±12	45-280
Fasting glucose, mg/dL	93±2	70-111
Fasting insulin, μU/mL	3.2±0.5	2-10

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Table 2

Arterial stiffness in response to MR Blockade

	Placebo	MR blockade	P value
Carotid artery compliance, $mm^2/mmHg$	0.150±0.013	0.149±0.014	0.8
Carotid artery distensibility, $10^{-3}/kPa$	23.1±1.8	23.3±1.7	0.8
Carotid artery β stiffness index	3.5±0.3	3.6±0.3	0.6
Carotid augmentation index, %	16.0±2.2	15.6±2.8	0.8
Aortic pulse wave velocity, m/s	9.17±1.19	8.92±1.19	0.5
Leg pulse wave velocity, m/s	13.45±0.45	12.81±0.47	0.3
Arm pulse wave velocity, m/s	11.43±0.62	11.73±0.68	0.7

Data are mean±SE.