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Aldosterone and Salt Loading Independently Exacerbate the Exercise Pressor Reflex in Rats

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Abstract

The sympathetic and pressor responses to exercise are exaggerated in hypertension. Evidence suggests that an overactive exercise pressor reflex (EPR) contributes to this abnormal responsiveness. The mechanisms underlying this EPR overactivity are poorly understood. An increasing body of evidence suggests aldosterone as well as excessive salt intake play a role in regulating resting sympathetic activity and blood pressure in hypertension. Therefore, each is a good candidate for the generation of EPR dysfunction in this disease. The purpose of this study was to examine whether excessive salt intake and/or chronic administration of aldosterone potentiate EPR function. Changes in mean arterial pressure (MAP) and renal sympathetic nerve activity (RSNA) induced by EPR stimulation were examined in vehicle and aldosterone treated (4 weeks via osmotic mini-pump) Sprague-Dawley rats given either water or saline (elevated salt load) to drink. Compared to vehicle/water-treated rats, stimulation of the EPR by muscle contraction evoked significantly greater increases in MAP in vehicle/saline, aldosterone/water and aldosterone/saline-treated animals (14±3, 29±3, 37±6, and 44±7mm Hg kg^{-1}, respectively, *P<0.01*). A similar RSNA response profile was likewise produced (39±11, 87±15, 110±20, and 151±25 % kg^{-1}, respectively, *P<0.01*). The pressor and sympathetic responses to the individual activation of the mechanically and chemically-sensitive components of the EPR were also augmented by both saline and aldosterone. These data provide the first direct evidence that both aldosterone and high salt intake elicit EPR overactivity. As such, each represents a potential

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DISCLOSURES

None.

mechanism by which sympathetic activity and blood pressure are augmented during exercise in hypertension.

Keywords

exercise pressor reflex; blood pressure; sympathetic nerve activity; renin angiotensin system

INTRODUCTION

The cardiovascular response to exercise is abnormally exaggerated in hypertensive patients and characterized by augmented increases in arterial blood pressure (BP), heart rate (HR), and sympathetic nerve activity (SNA) [1]. Since such responses have been shown to be associated with elevated risks for myocardial ischemia, myocardial infarction, cardiac arrest and/or stroke during and after physical activity, elucidating the cause of the cardiovascular hyper-excitability is clinically as well as physiologically important [2].

Afferent signals from working skeletal muscle are an important source of neural input to the brain stem during exercise and contribute significantly to the regulation of sympathetic outflow as well as the cardiovascular system during physical activity [3]. These contraction-induced signals, which comprise the skeletal muscle exercise pressor reflex (EPR), are generated by stimulation of group III (predominantly mechanically-sensitive A-δ fibers associated with the muscle mechanoreflex) and IV (primarily chemically-sensitive C fibers associated with the muscle metaboreflex) skeletal muscle afferents [3, 4]. It has been extensively demonstrated in a number of animal models of human hypertension that the EPR is overactive in the disease contributing significantly to the exaggerated increases in SNA and BP that manifest during exercise [5–7]. That being stated, the mechanisms underlying the pathogenesis of EPR dysfunction in hypertension have not been fully established.

Aldosterone is well known to contribute to the development of hypertension. Circulating aldosterone penetrates the blood-brain barrier at concentrations paralleling those found in plasma [8, 9]. Aldosterone has been shown to act centrally stimulating the sympathetic nervous system [10, 11]. Earlier studies demonstrated that direct infusion of aldosterone into the cerebral ventricles causes a sustained increase in BP and renal SNA (RSNA) in rats and dogs [12–16]. As such, aldosterone represents a potential mechanistic candidate for the generation of EPR overactivity.

Like aldosterone, high salt intake has also been shown to activate the sympathetic nervous system by increasing sodium concentrations in cerebrospinal fluid and neural tissue [17, 18]. Moreover, a recent study suggests that increased salt intake augments EPR function in rats [19] establishing this mechanism as an additional potential candidate for the generation of muscle reflex overactivity in hypertension. Importantly, it has been suggested that the central pressor action of aldosterone is observed only in the presence of sodium excess or in salt-sensitive animals [15, 20]. As such, if aldosterone does indeed augment EPR activity its action may be amplified by the presence of increased sodium.

Therefore, this study was designed to test the hypotheses that i) chronic systemic administration of aldosterone potentiates EPR function and ii) aldosterone-induced EPR overactivity is exacerbated by concomitant salt-loading. In addition, studies were performed to confirm and support reports that increased sodium intake alone elicits EPR dysfunction. To test these hypotheses, we examined cardiovascular and sympathetic responses to activation of the EPR, as well as its individual mechanically and chemically-sensitive components, in vehicle and aldosterone treated Sprague-Dawley rats given either water or saline to drink.

METHODS

For a complete description of the Materials and Methods see the online-only Data Supplement.

Animal models—Experiments were performed on 46 male Sprague-Dawley rats (11–12 wk, 310–350 g) Under isoflurane anesthesia, osmotic minipumps (2ML4, ALZET) were implanted subcutaneously for 28 days to deliver 250 μg kg^{-1} day^{-1} doses of aldosterone (n = 23) or vehicle (n = 23). The animals in each group were assigned to drink normal water or 0.9% NaCl saline (vehicle/water: n = 11; vehicle/saline: n = 12; aldosterone/water: n =12; and aldosterone/saline: n =11). The procedures outlined were approved by the Institutional Animal Care and Use Committee. All studies were conducted in accordance with the US Department of Health and Human Services NIH *Guide for the Care and Use of Laboratory Animals*.

Experimental Protocols

MAP, HR, and RSNA were continuously measured at rest and during stimulation of either the EPR, the muscle mechanoreflex or muscle metaboreflex.

Muscle Reflex Stimulation—The EPR was stimulated by contracting the triceps surae muscles of the right hindlimb for 30s via electrical stimulation of isolated L_4 and L_5 ventral roots. Constant current stimulation was used at a 3 times motor threshold (i.e. the minimum current required to produce a muscle twitch) with a pulse duration of 0.1 ms at 40 Hz. Activation of the EPR in this manner stimulates mechanically and chemically-sensitive skeletal muscle afferent fibers concomitantly. To preferentially activate mechanically sensitive afferent neurons, the triceps surae muscles were passively stretched. Isolated activation of chemically sensitive fibers was achieved by administering graded concentrations of capsaicin into the arterial supply of the hindlimb.

Statistical Analyses

Data were analyzed using two-way ANOVA (aldosterone × saline) and three-way ANOVA (aldosterone × saline × administration period, aldosterone × saline × capsaicin concentration). When appropriate, a post hoc Fisher's PLSD test was used to identify differences between specific group means. The significance level was set at $P < 0.05$. Results are presented as means ± S.E.M.

RESULTS

Morphometric characteristics and plasma aldosterone concentrations for each experimental are presented in Table 1. Body weight was lower in the aldosterone/saline treated animals compared to all other groups. Heart weight to body weight ratios and heart weight to tibial length ratios were significantly higher in aldosterone treated groups than vehicle treated animals. Plasma aldosterone concentrations in aldosterone/water as well as aldosterone/saline treated groups were markedly larger after 4 weeks of aldosterone administration compared to vehicle treated animals.

Four weeks of aldosterone administration, but not saline intake, significantly increased conscious resting systolic arterial pressure (SAP) measured by tail cuff (Fig. 1). Concomitant high salt intake did not further augment the increases in baseline SAP induced by aldosterone administration (aldosterone × saline: $P = 0.6005$).

The pressor, tachycardic and sympathetic responses to stimulation of the EPR during static muscle contraction were augmented by salt intake alone as well as aldosterone administration alone compared to control animals (Fig. 2; aldosterone effect: $P < 0.01$ and saline effect: $P < 0.05$ for MAP and RSNA). Importantly, the effects of aldosterone on the EPR-induced rise in MAP, HR, and RSNA were not altered by sodium intake (all interaction p value > 0.1).

High salt intake alone as well as aldosterone alone significantly enhanced the changes in MAP, HR and RSNA in response to stimulation of the muscle mechanoreflex during passive muscle stretch (Fig. 3; aldosterone effect: $P < 0.01$ and saline effect: $P < 0.05$). The effects of aldosterone on the mechanoreflex-induced HR response, but not the MAP or RSNA responses, was potentiated by high sodium intake.

High salt intake alone and aldosterone alone exacerbated the cardiovascular response to stimulation of the muscle metaboreflex during capsaicin administration (Fig 4.). The effects of aldosterone administration on the metaboreflex-induced elevation in MAP, HR, and RSNA was not altered by concomitant sodium intake (all interaction p value > 0.1).

Additional results are reported in the online-only Data Supplement.

DISCUSSION

The major new findings from this investigation were i) chronic aldosterone administration significantly augmented EPR activity; ii) aldosterone-induced EPR dysfunction was mediated by both the mechanically and chemically-sensitive components of the EPR; and iii) the deleterious actions of aldosterone on EPR activity were not appreciably amplified by concomitant high sodium intake. In agreement with a previous report, it was also demonstrated that salt loading alone significantly enhanced the sympathetic and cardiovascular responses to activation of the EPR. These findings establish that both excessive levels of aldosterone and high salt intake can each individually induce EPR overactivity. As such, each may contribute significantly to the exaggerated elevations in sympathetic activity and blood pressure generated during exercise in this disease.

Previous studies have demonstrated that aldosterone increases renal sympathetic nerve discharge and BP in the resting condition [15, 21]. However, the influence of aldosterone on sympathetic regulation during exercise has not been investigated. To the best of our knowledge, this is the first report showing that aldosterone alters sympathetic and cardiovascular responses to activation of the EPR during physical stress. Interestingly, the EPR overactivity demonstrated was mediated by both functional components of the reflex: the muscle mechanoreflex and metaboreflex. The mechanisms underlying aldosterone-induced enhancements in mechano- and metaboreflex function remain unknown. However, It has been reported that aldosterone with salt loading for 4 weeks results in muscle atrophy [22]. It has also been demonstrated that the pressor response to passive stretch is significantly greater in atrophied muscle compared to healthy muscle [23]. In the current investigation, aldosterone administration with high salt intake significantly decreased body mass (Table 1) while likewise reducing the developed peak tension during muscle contraction (Table S2). The EPR overactivity generated in aldosterone treated animals might be explained by sensitization of the muscle reflexes as a result of saline/aldosterone induced-muscle atrophy. However temping to conclude, this would not explain the EPR dysfunction that manifested in rats treated only with aldosterone. Aldosterone alone is also known to induce cardiomyopathy [22, 24]. Previous studies in rats and patients with congestive heart failure have demonstrated enhanced EPR activity via selective mechanoreflex sensitization [25–28]. In our study, chronic aldosterone administration induced left ventricular hypertrophy as evidenced by increased heart weight to body weight ratios as well as heart weight to tibial length ratios. However, the lung weight in aldosterone treated rats was not increased suggesting that congestive heart failure had not developed. Thus, although the hypertrophic cardiomyopathy induced by aldosterone administration may contribute to the generation of EPR dysfunction to some extent it seems unlikely to be the primary cause. Other possibilities include aldosterone-induced impairments in baroreflex-mediated inhibition of SNA (chronic intracerebroventricular infusion of aldosterone has been shown to inhibit arterial baroreflex control of RSNA and HR) [20] and direct modulation by aldosterone of central sympathoexcitatory pathways [20].

In our study, high salt intake alone significantly augmented the MAP, HR and RSNA responses to activation of the EPR (Fig. 2). These findings are consistent with a recent report demonstrating that increased dietary salt intake enhances pressor and cardioaccelerator responses to muscle contraction in rats [19]. Our data extended these previous findings by demonstrating that EPR dysfunction in saline treated rats is mediated by both mechanoreflex and metaboreflex overactivity. Accumulating reports indicate that salt intake does not alter vasoconstrictor responses to sympathetic stimulation in rats [19, 29–31]. Thus, it is logical to postulate that salt-induced EPR overactivity results from the sensitization of brainstem circuits in the muscle reflex pathway. Sensitization of these circuits could cause the abnormally large elevations in sympathetic output observed during muscle reflex activation. However plausible, the exact downstream mechanisms underlying such changes remain undetermined. High salt intake has been shown to increase the concentration of sodium in cerebral spinal fluid and brain tissue which could evoke central sympathetic activation via stimulation of epithelial sodium channels (ENaC) [20, 32.33]. Specifically, it has been suggested that sodium acts on neurons within the organum vasculosum of the lamina

terminalis to enhance the responsiveness of sympathetic motor neurons emanating from the rostral ventrolateral medulla (RVLM) within the brainstem [34]. Continued research in this area is needed to determine whether these pathways underlie high salt intake-induced EPR dysfunction.

In the current investigation, the excitatory effect of aldosterone on EPR activity was not dependent upon the level of salt intake. Although it has been suggested that the hypertensive and sympathoexcitatory action of aldosterone requires the presence of excess sodium, we found a strong independent action of aldosterone on EPR activity that was not appreciably affected by increased salt ingestion [15, 20]. This suggests that aldosterone and salt loading may accentuate EPR function through similar pathways. The RVLM, an established cardiovascular regulatory nuclei within the brainstem, is a good candidate for the mediation of this EPR overactivity. Increased dietary salt intake enhances sympathetic responsiveness to stimulation of the RVLM [35]. Furthermore, a neurophysiological study has clearly demonstrated that aldosterone activates RVLM neurons through mineralocorticoid receptors (MR) as well as ENaCs [36]. Thus, it is plausible that aldosterone and salt loading alter neural activity in the RVLM through MR and/or ENaCs. The paraventricular nucleus (PVN) of the hypothalamus, known to be an important contributor to autonomic cardiovascular control, is another reasonable candidate. It comprises ~70% of the pre-ganglionic fibers by-passing the RVLM [37] and likewise expresses MR [38]. Because the pre-collicular decerebration performed in the current study removes the hypothalamus, the PVN was unlikely to contribute substantially to the abnormal EPR function observed in the present investigation. However, we cannot exclude the possibility that chronic administration of aldosterone could have induced permanent alterations in the function of brainstem neurons prior to removal of the PVN contributing to the results reported. Although speculative in nature, it is tempting to suggest that sodium and aldosterone affect these cardiovascular regulatory regions of the brain and in this manner independently alter EPR function.

It should be noted, in the current study concomitant high salt intake did not further augment the increases in baseline SAP induced by aldosterone. This finding is inconsistent with a previous study using rats in which the effects of intracerebroventricular as well as subcutaneous aldosterone administration on blood pressure were examined [16]. The discrepancy may be partly explained by the difference in experimental designs between studies. For example, in the current study a higher dose of aldosterone was utilized and the kidneys were not removed. Nevertheless, the findings clearly support the contention that aldosterone and high salt intake alter EPR function and may do so via similar mechanisms.

PERSPECTIVES

Excessive BP elevation during exercise has been shown to contribute to impaired exercise tolerance in hypertensive patients even in the absence of coronary artery disease or left ventricular dysfunction [39–42]. Furthermore, numerous epidemiological studies have demonstrated that exercise blood pressure predicts development of left ventricular hypertrophy, stroke, myocardial infarction, and death [43–47] independent of resting BP. Our study in rodents suggests a potential role for both aldosterone and dietary salt intake in modulating the sympathetically mediated BP response to exercise via alterations in reflexes

originating from the skeletal muscle. Based on these findings, further studies in humans are needed to confirm if salt restriction and MR blockade constitute two independent effective strategies in attenuating the augmented pressor response to exercise in hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NOVELTY AND SIGNIFICANCE

What Is New?

Although the sympathetically mediated cardiovascular response to physical activity in hypertensive patients is heightened as compared to healthy subjects, the underlying mechanisms are poorly understood. Accumulating evidence suggests that aldosterone and high dietary salt intake play a role in regulating baseline sympathetic outflow in hypertension. However, whether each contributes to the generation of the excessive sympathetic and cardiovascular responses to exercise in this disease remains unknown.

What Is Relevant?

The findings indicate that controlling salt intake and/or treating excessive levels of aldosterone may improve blood pressure regulation during exercise in hypertension.

Summary

The present findings demonstrate that systemic administration of aldosterone and high dietary salt intake independently potentiate the function of the skeletal muscle exercise pressor reflex; a reflex which regulates, in part, the rise in sympathetic nerve activity and blood pressure during physical exertion and is known to be overactive in hypertension.

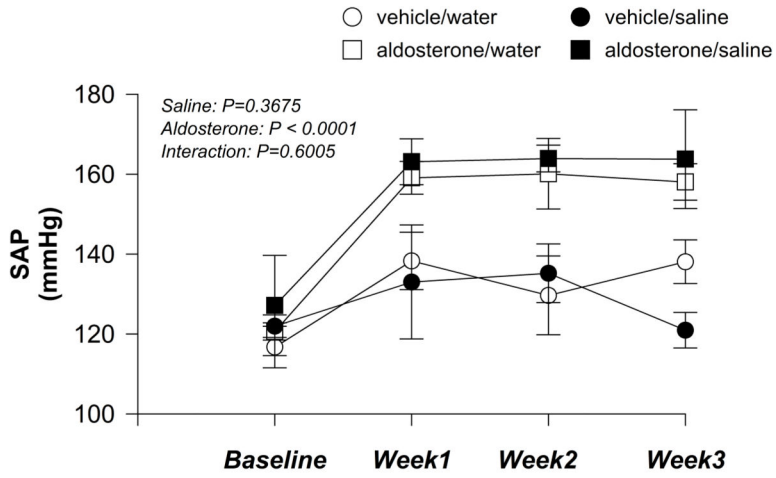

Figure 1.

Conscious systolic arterial pressure (SAP) measured by tail cuff in vehicle/water, vehicle/saline, aldosterone/water and aldosterone/saline rats before and 3 weeks after mini-pump implantation (n = 5 in each group). Saline: 0.9% NaCl.

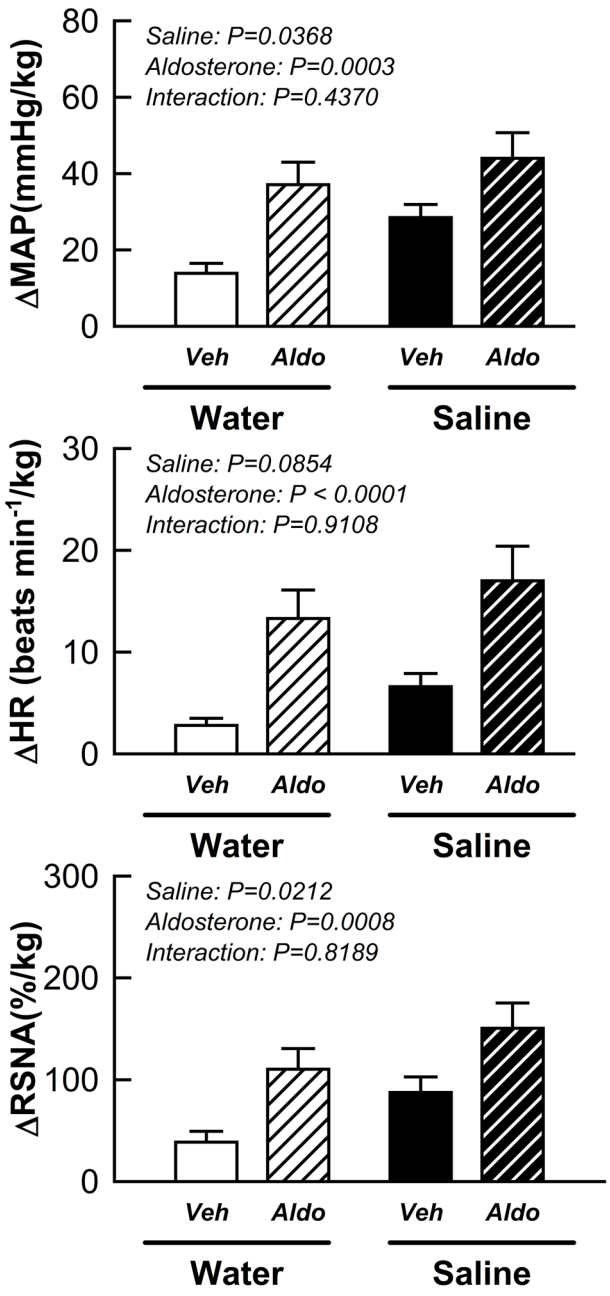

Figure 2.

Cardiovascular and sympathetic responses to activation of the EPR during static muscle contraction in vehicle/water, vehicle/saline, aldosterone/water and aldosterone/saline rats. Veh: vehicle; Aldo: aldosterone. Saline: 0.9% NaCl.

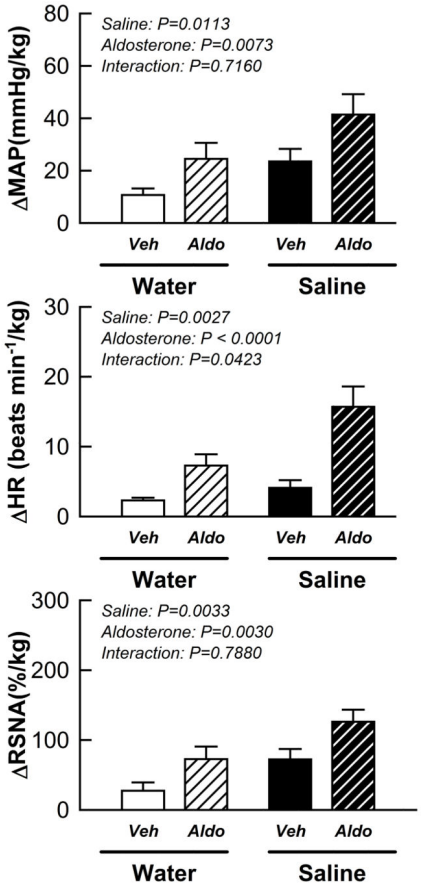

Figure 3.

Cardiovascular and sympathetic responses to activation of the mechanically sensitive component of the EPR in vehicle/water, vehicle/saline, aldosterone/water and aldosterone/saline rats. Veh: vehicle; Aldo: aldosterone. Saline: 0.9% NaCl.

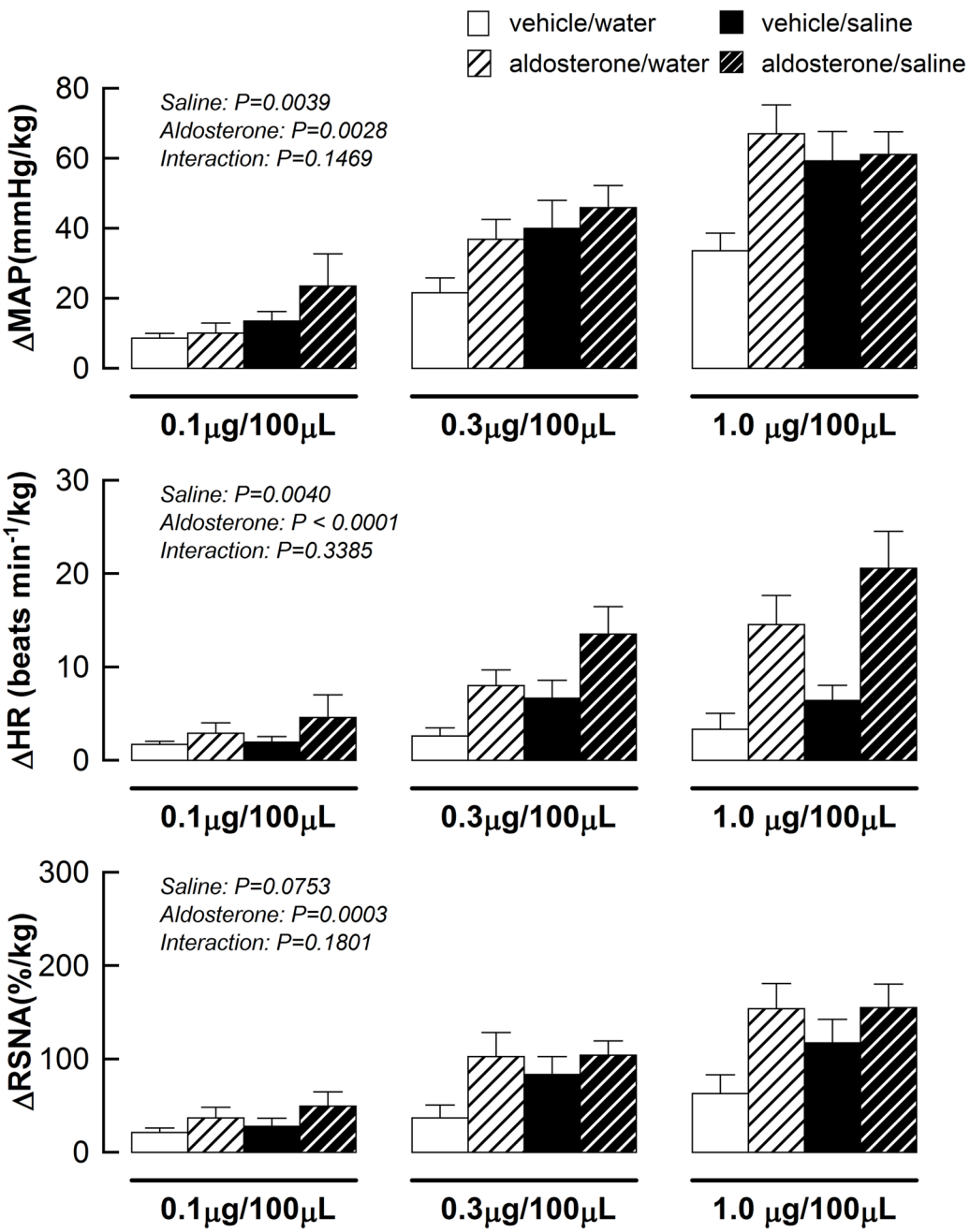

Figure 4.

Cardiovascular and sympathetic responses to activation of the metabolically sensitive component of the EPR in vehicle/water, vehicle/saline, aldosterone/water and aldosterone/saline rats. Saline: 0.9% NaCl.

Table 1

Morphometric characteristics and plasma aldosterone.

	Water		Saline	
Variables	**Vehicle**	**Aldosterone**	**Vehicle**	**Aldosterone**
n	11	12	12	11
Body weight (g)	416 ± 4	429 ± 15	412 ± 5	366 ± 8 *†‡
Heart weight/body weight (mg g^{-1})	2.62 ± 0.04	2.88 ± 0.07*†	2.64 ± 0.07	3.23 ± 0.11 *†‡
Heart weight/tibial length (mg mm^{-1})	27.4 ± 0.5	31.2 ± 0.8*†	27.5 ± 0.7	29.5 ± 0.8 *†
Lung weight/body weight (mg g^{-1})	5.66 ± 0.34	6.35 ± 0.79	5.96 ± 0.26	6.53 ± 0.48
Plasma aldosterone concentration (ng 100 mL^{-1})	10 ± 1	736 ± 503*†	8 ± 4	444 ± 117*†

Values are means ± S.E.M.

*$P < 0.05$ compared to vehicle/water.

†$P < 0.05$ compared to vehicle/saline.

‡$P < 0.05$ compared to aldosterone/water. Saline: 0.9% NaCl.