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Estrogen status and the renin angiotensin aldosterone system

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O’Donnell E, Floras JS, Harvey PJ. Estrogen status and the renin angiotensin aldosterone system. Am J Physiol Regul Integr Comp Physiol 307: R498–R500, 2014. First published June 18, 2014; doi:10.1152/ajpregu.00182.2014.—The renin-angiotensin-aldosterone system (RAAS) is integrally involved in multiple cardiovascular physiological processes including arterial blood pressure (BP) regulation. Over activity of the RAAS has been implicated in the pathogenesis of a number of cardiovascular disease entities, including hypertension. Several lines of evidence suggest estrogen favorably modulates the RAAS. Conversely, estrogen deficiency due to menopause may contribute to over activity of the RAAS. Of importance, estrogen deficiency in women is not exclusive to the postmenopausal period. Functional hypothalamic amenorrhea is a reversible cause of premenopausal hypoestrogenemia. In contrast to postmenopausal women (PMW), premenopausal women with exercise-associated functional hypothalamic amenorrhea demonstrate decreased, not increased, resting BP compared with their estrogen-replete eumenorrheic counterpart. In this review we briefly examine the effects of estrogen status on the RAAS and present the hypothesis that the RAAS is altered in physically active women with functional hypothalamic amenorrhea.

amenorrhea; estrogen; energy deficiency; exercise; ovarian disruption

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) pathway consists of circulating and local/tissue renin, angiotensin I (ANG I), ANG I-converting enzyme (ACE), angiotensin II (ANG II), and ANG II type 1 (AT1R) and type II (AT2R) receptors. Activation of AT1R by ANG II mediates the physiological effects of the RAAS, including regulation of water and electrolyte homeostasis, and systemic vascular resistance, two major determinants of cardiac output and arterial blood pressure (BP). Chronic activation of AT1R is also associated with vascular dysfunction, vascular inflammation, arterial wall thickening, myocardial fibrosis, and disease states such as hypertension, atherosclerosis, and heart failure (14). Conversely, binding of ANG II to the AT2R opposes the actions of AT1R, eliciting vasodilation, anti-proliferative, and anti-fibrotic effects on the vascular smooth muscle cells and the heart and enhancing pressure natriuresis (5, 14). More recently, novel RAAS axes have also been identified, including the ACE2, ANG-(1–7), and the MAS receptor axis and the ANG IV, AT4 receptor and insulin-regulated aminopeptidase axis (13). While the actions of these novel RAAS axes have yet to be fully delineated, the putative physiological effects of the ANG-(1–7) axis are reported to be similar to that of AT2R (14).

Evidence suggests estrogen is involved in regulation of multiple RAAS pathways. The following review considers how the RAAS may be influenced by estrogen status in premenopausal and postmenopausal women (PMW). This review also postulates the effects of hypoestrogenemia on the RAAS in physically active premenopausal women with functional hypothalamic amenorrhea.

RAAS and the Menstrual Cycle

RAAS modulation varies across the menstrual cycle. For example, plasma renin activity and circulating ANG II and aldosterone levels are elevated during the luteal (high estrogen and high progesterone) compared with the follicular (low estrogen and low progesterone) phase (2). Despite elevated circulating RAAS components during the luteal phase, mean arterial BP is not maintained during simulated orthostatic stress compared with the follicular phase (2). This observation is postulated to reflect estrogen-mediated decreases in tissue responsiveness to circulating RAAS during the luteal phase and/or the competing vasodilatory and sympathoinhibitory effects of estrogen (12). Given that ovarian hormones fluctuate across the menstrual cycle, the independent effects of endogenous estrogen and progesterone per se on the RAAS largely remain unclear.

RAAS and Exogenous Estrogen

In premenopausal women, combination estrogen and progesterone oral contraceptive formulations increase plasma
renin activity, and circulating angiotensinogen, ANG II, and aldosterone concentrations (7). Similarly, oral estrogen therapy in PMW increases circulating concentrations of angiotensinogen (4, 6), ANG I and ANG II (4, 6), decreases circulating ACE (6), and variably alters plasma renin concentrations (4, 6). Despite increases in RAAS components, arterial BP is decreased or unaltered (4, 6). Although mechanisms of action are not clear, estrogen is known to upregulate gene expression of angiotensinogen (5), and in PMW, estrogen therapy increases circulating cardiac atrial natriuretic peptide (ANP), a potent vasodilator that is also involved in fluid, sodium, and potassium homeostasis (8). Animal studies also report 17 β-estradiol administration increases circulating ANG-(1–7) and renal expression of AT2R and ACE2, yet decreases renal expression of AT1R (5). Thus the composite effect of estrogen on the RAAS is complex; potentially deleterious increases in circulating components of the classic RAAS may be counterbalanced by altered AT1R/AT2R receptor expression, and vasodilator components including ANG-(1–7) and ANP may be increased. Such effects may influence the vasoconstricting/vasodilating balance in favor of vasodilation.

RAAS and Estrogen Deficiency Due to Menopause

Studies report similar circulating concentrations of angiotensinogen, renin, ANG II, and aldosterone in normotensive PMW compared with eumenorheic premenopausal women (4). In contrast, simulated orthostatic stress acutely activates the RAAS in estrogen-replete premenopausal women but not in PMW. However, after administration of estrogen, RAAS responsiveness is restored in PMW to a magnitude similar to that observed in premenopausal women (4). Notably, despite RAAS activation during orthostatic stress with estrogen therapy, systolic BP is lower than that observed without estrogen therapy (4). Ovariectomy in animal models of estrogen deficiency elicits upregulated tissue expression of ACE (11) and AT1R (5) and decreased tissue expression of AT2R (14). Thus hypoestrogenemia appears to exert competing RAAS effects, with the potentially cardiovascular favorable effects of lowering circulating RAAS components possibly being offset by a higher AT1R:AT2R.

RAAS and Estrogen Deficiency Due to Functional Hypothalamic Amenorrhea

Functional hypothalamic amenorrhea in weight-stable physically active women has been causally related to energy deficiency in association with a high-energy expenditure often times combined with subtle caloric-intake deficits (9). Our group has reported several cardiovascular perturbations in these women, including endothelial dysfunction, decreased calf blood flow, and increased regional vascular tone (9). Despite hypoestrogenemia and increased vascular tone, physically active women with functional hypothalamic amenorrhea women demonstrate lower, not higher, resting BP than their eumenorheic counterpart (9). Although not yet confirmed, this observation suggests the RAAS may be altered in these women, possibly due to hypoestrogenemia. However, it is conceivable energy deficiency and/or exercise training also modulates the RAAS in this group of women (see Fig. 1). In humans, caloric restriction lowers circulating basal renin and aldosterone (10), and aerobic exercise training attenuates ANG II-induced vaso-

constriction, possibly through downregulation of vascular AT1R expression (1). In animals, endurance training reduces tissue ANG II and ACE and increases cardiac ACE2 and ANG-(1–7) expression (3). Thus it is likely that complex interplay between energy deficiency, exercise training, and hypoestrogenemia may modulate the RAAS in physically active women with functional hypothalamic amenorrhea.

Perspectives and Significance

Overactivation of the RAAS is implicated in the pathogenesis of hypertension. Estrogen status influences the RAAS. Both endogenous and exogenous estrogen alter the balance between the vasoconstricting and vasodilating arms of the RAAS, favoring vasodilation. Conversely, hypoestrogenemia due to menopause upregulates the vasoconstricting arm of the RAAS. In contrast, exercise-trained premenopausal women with chronic hypoestrogenemia due to energy deficiency demonstrate lower resting arterial BP than that of their estrogen-replete counterpart. In this review we present the hypothesis that the pressor effects of the RAAS may be offset in these women due to the upregulatory effects of exercise training and/or caloric restriction on the vasodilating arm of the RAAS. While this postulate remains to be confirmed, the long-term clinical cardiovascular consequences of competing factors such as low arterial BP yet endothelial dysfunction in
physically active women with functional hypothalamic amenorrhea await delineation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: E.O., J.S.F., and P.J.H. conception and design of research; E.O. prepared figures; E.O. drafted manuscript; J.S.F. and P.J.H. edited and revised manuscript; J.S.F. and P.J.H. approved final version of manuscript.

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