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COMMENTARY

Women are different: the role of coupling factor 6 in blood pressure regulation

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Blood pressure (BP)-related diseases, particularly, hypertension, coronary heart disease, heart failure and stroke are the leading causes of morbidity and mortality. Worldwide, elevated BP accounts for 47% of coronary heart disease cases and 54% of stroke incidences.[1] Moreover, about 13% of total deaths worldwide are a result of hypertension. The excessive intake of salt has a major role in the pathogenesis of hypertension. To date, over 50 randomized trials have tested the effects of sodium reduction on BP in adults, with the overall consensus that sodium intake has a statistically significant, progressive and dose-dependent relationship with BP. A daily modest reduction of 100 mmol (6 g of salt) has been shown to significantly reduce systolic and diastolic BP in both the hypertensive and normotensive subjects.[2] In this issue of *Hypertension Research*, Izumiyama *et al.*[3] show that estrogen replacement has a cardioprotective function in ovariectomized females under a high-salt diet (HSD). Furthermore, they report on the mechanism whereby coupling factor 6 (CF6) overexpression increases salt-sensitive hypertension, resulting in enhanced cardiac systolic dysfunction.

The National Health and Nutrition Examination Survey showed that more men than women have hypertension until 45 years of age.[4] The prevalence and severity of hypertension upsurges significantly with age in women, such that more women than men are hypertensive after 65 years of age.[4,5] Izumiyama *et al.* show that male transgenic mice overexpressing CF6 (TG) develop hypertension sooner than females when fed HSD. Although TG males showed increased systolic BP beginning at 20 weeks of HSD, it was not until 60 weeks of HSD that the TG females demonstrated elevated systolic BP. Interestingly, wild-type mice, both male and female, did not show hypertension when fed HSD.

In a second experiment, ovariectomized young TG females were treated with estrogen replacement (0.18 mg estradiol) or placebo, 1 week post-surgery under HSD. They showed a marked increase in systolic BP of TG mice that were ovariectomized, compared with animals that underwent sham surgery. In addition, left ventricular fractional shortening, a measurement of cardiac function, decreased in ovariectomized females, but this effect was not observed when ovariectomized females received estrogen replacement. A European study for diagnosis of hypertension showed that the prevalence of hypertension in postmenopausal women was more than twice that in premenopausal women.[6] These findings suggest that changes in ovarian hormone levels are related to changes in BP. Izumiyama *et al.* results are in agreement with these findings. Over the last 30 years, many studies involving BP and hormone replacement therapy have been conducted, but the findings have been inconsistent. In normotensive women treated with hormone replacement therapy, BP has been shown to decrease,[7] increase[8] or remain unaffected.[9] A study comprising 809 postmenopausal women with and without hysterectomy did not show an association between hysterectomy and increased risk of cardiovascular disease (CVD).[10] Contrarily, a Women's Health Initiative observational study compared CVD risk factors between postmenopausal women who had and had not undergone hysterectomy, with or without ovariectomy, in a total of 89 914 patients.[11] They concluded that women with a hysterectomy had a worse risk profile and higher prevalence and incidence of CVD. Nevertheless, they also reported that multivariate models suggested that CVD risks were rather due to the more adverse initial risk profile of women who had undergone hysterectomy, and not that hysterectomy was the major determinant for CVD.[11]

In the Izumiyama study, CF6 TG mice showed elevated levels of activated Rac1, a member of the Rho family GTPases, leading to salt-sensitive hypertension.[3] CF6 is a component of the intrinsic membrane domain (F_0) of ATP synthase, which is considered to be essential for energy transduction.[12] Recently CF6 has been identified to have multiple extracellular roles as a circulating hormone.[12] CF6 increases arterial BP in rats, which is consistent with high levels of CF6 seen in the plasma of patients diagnosed with hypertension.[13] Studies where CF6 is quantified in pre or postmenopausal women, however, have not been carried out. CF6 functions are believed to be mediated by binding to the plasma membrane-bound ATP synthase, ecto-F_1F_0 complex, resulting in proton import and acidosis, which will in turn increase activated Rac1. Although the authors show a correlation between estrogen and Rac1 activation, the exact mechanism was not explored. In recent studies, cardiac-specific overexpression of constitutively activated Rac1-induced atrial fibrillation in mice via activation of the superoxide-producing NADPH-oxidase, indicating the importance of Rac1 in reactive oxygen species (ROS) production.[14] A decrease of Rac1 expression by estrogen was completely blocked in the

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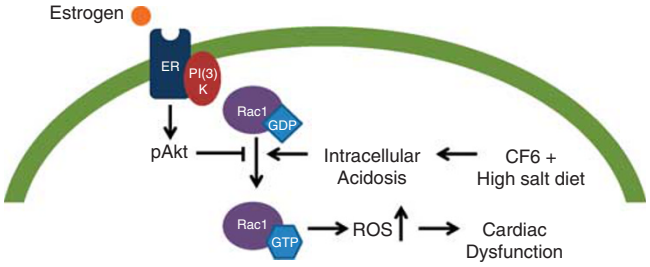

Figure 1 A high-salt diet can increase intracellular acidosis through CF6 proton import; acidosis then stimulates Rac 1 and increases reactive oxygen species (ROS) formation. Increased ROS can lead to cardiac dysfunction. In the presence of estrogen, the estrogen receptor (ER) can bind to the regulatory subunit, p85a, of phosphatidylinositol-3-OH kinase (PI(3)K), inducing enhanced activation of Akt. Akt is involved in cellular survival pathways, by inhibiting apoptotic processes and activated Akt can phosphorylate Rac1 at Ser71 reducing Rac1 activation. This in turn would reduce ROS-induced injury to the cardiovascular system as well as lower salt retention.

presence of a nonselective estrogen receptor (ER) antagonist, suggesting a receptor-mediated event.[15] *Ex vivo* studies have shown that ER can bind to the regulatory subunit, p85a, of phosphatidylinositol-3-OH kinase leading to enhanced activation of Akt in the presence of estrogen.[16] Akt is involved in cellular survival pathways, by inhibiting apoptotic processes and activated Akt can phosphorylate Rac1 at Ser71 reducing Rac1 activation.[17] This in turn would reduce ROS-induced injury to the cardiovascular system as well as lower salt retention (Figure 1). Although Izumiyama *et al.* showed that estrogen replacement, in ovariectomized mice, would decrease the activation of Rac1, no connection with Akt was evaluated. Further *in vivo* studies would be needed in order to validate the decrease in activated Rac1 to be due to activation of Akt.

The effect of menopause on hypertension is controversial, masked by the effects of aging and clusters of other CVD risk factors, such as body weight and lipid levels. Further, studies have shown that with age cardiac extracellular matrix accumulates to induce a modest cardiac dysfunction.[18] Whether estrogen replacement has a role in protecting from cardiac extracellular matrix accumulation in postmenopausal females would provide additional insight into this complex issue. The study by Izumiyama *et al.* emphasizes the usefulness of mice models; by using transgenic mice overexpressing CF6 to establish a connection between CF6 levels and salt-sensitive hypertension. In summary, Dr Izumiyama *et al.* provide further support for the concept that hormone replacement, given during the postmenopausal period, mitigates adverse cardiac effects caused by increased levels of activated Rac1.

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