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Research Report

The accumulation of brain water-free sodium is associated with ischemic damage independent of the blood pressure in female rats

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ABSTRACT

Estrogen deficiency worsens ischemic stroke outcomes. In ovariectomized (OVX^+) rats fed a high-salt diet (HSD), an increase in the body Na^+/water ratio, which characterizes water-free Na^+ accumulation, was associated with detrimental vascular effects independent of the blood pressure (BP). We hypothesized that an increase in brain water-free Na^+ accumulation is associated with ischemic brain damage in OVX^+/HSD rats. To test our hypothesis we divided female Wistar rats into 4 groups, OVX^+ and OVX^- rats fed HSD or a normal diet (ND), and subjected them to transient cerebral ischemia. The brain Na^+/water ratio was increased even in OVX^+/ND rats and augmented in OVX^+/HSD rats. The increase in the brain Na^+/water ratio was positively correlated with expansion of the cortical infarct volume without affecting the BP. Interestingly, OVX^+ was associated with the decreased expression of ATP1α3, a subtype of the Na^+ efflux pump. HSD increased the expression of brain Na^+ influx-related molecules and the mineralocorticoid receptor (MR). The pretreatment of OVX^+/HSD rats with the MR antagonist eplerenone reduced brain water-free Na^+ accumulation, up-regulated ATP1α3, down-regulated MR, and reduced the cortical infarct volume. Our findings show that the increase in the brain Na^+/water ratio elicited by estrogen deficiency or HSD is associated with ischemic brain damage BP-independently, suggesting the importance of regulating the accumulation of brain water-free Na^+. The up-regulation of ATP1α3 and the down-regulation of MR may provide a promising therapeutic strategy to attenuate ischemic brain damage in postmenopausal women.

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1. Introduction

The functional outcome after acute ischemic stroke is poorer in women, especially postmenopausal women, than men (Turtzo and McCullough, 2008). Epidemiological studies have shown that a high-salt intake is a risk factor for stroke (Li et al., 2012; Strazzullo et al., 2009), a leading cause of morbidity and mortality worldwide. Elsewhere we demonstrated that in ovariectomized (OVX^+) rats fed a high-salt diet (HSD), the increase in the body Na^+/water ratio was associated with the formation of cerebral aneurysms without a rise in the blood pressure (BP) (Matsushita et al., 2012). Excessive salt intake is thought to induce hypertension by Na^+ and concomitant water retention. However a large amount of Na^+ can be accumulated without accompanying water retention in the form of water-free Na^+ (Heer et al., 2000), which can be characterized by an increase in the Na^+/water ratio. The skin interstitium is a water-free Na^+ reservoir that can buffer the impact of Na^+ accumulation on the intravascular volume (Coffman, 2011).

Compared to age-matched men, women are resistant to the hypertensive effects of dietary salt (Titze et al., 2003). Although the detailed mechanisms underlying this sex difference remain obscure, they may involve disturbance of the function of the renin–angiotensin–aldosterone system (RAAS) (Rands et al., 2012) and oxidative stress (Sartori-Valinotti et al., 2008). Estrogen deficiency exacerbates experimental ischemic brain damage in rats (Shimada et al., 2011). As the expression of Na^+/K^+-ATPase is modified by estrogen (Palacios et al., 2004), the down-regulation of Na^+/K^+-ATPase may be partly involved in the pathophysiology of brain ischemia (Pimentel et al., 2013). Elsewhere we demonstrated that the incidence of cerebral aneurysms was reduced in rats treated with the angiotensin II type 1 receptor blocker olmesartan (Matsushita et al., 2012) or the mineralocorticoid receptor (MR) antagonist eplerenone (EPL) (Tada et al., 2009). Olmesartan decreased the body Na^+/water ratio and increased the expression of ATP1α2, a subtype of the Na^+ efflux pump, in the cerebral blood vessels of OVX^+/HSD rats (Matsushita et al., 2012) and EPL reduced the sodium intake of OVX^+/HSD rats without affecting the BP (Tada et al., 2009). These findings suggest that, apart from their hypotensive action, they may have vasoprotective effects regulating the accumulation of water-free Na^+.

Based on our findings and those of others we hypothesized that the accumulation of brain water-free Na^+ in estrogen-deficient female rats is associated with ischemic brain damage. To test our hypothesis and to verify the mechanisms underlying the accumulation of brain water-free Na^+ we

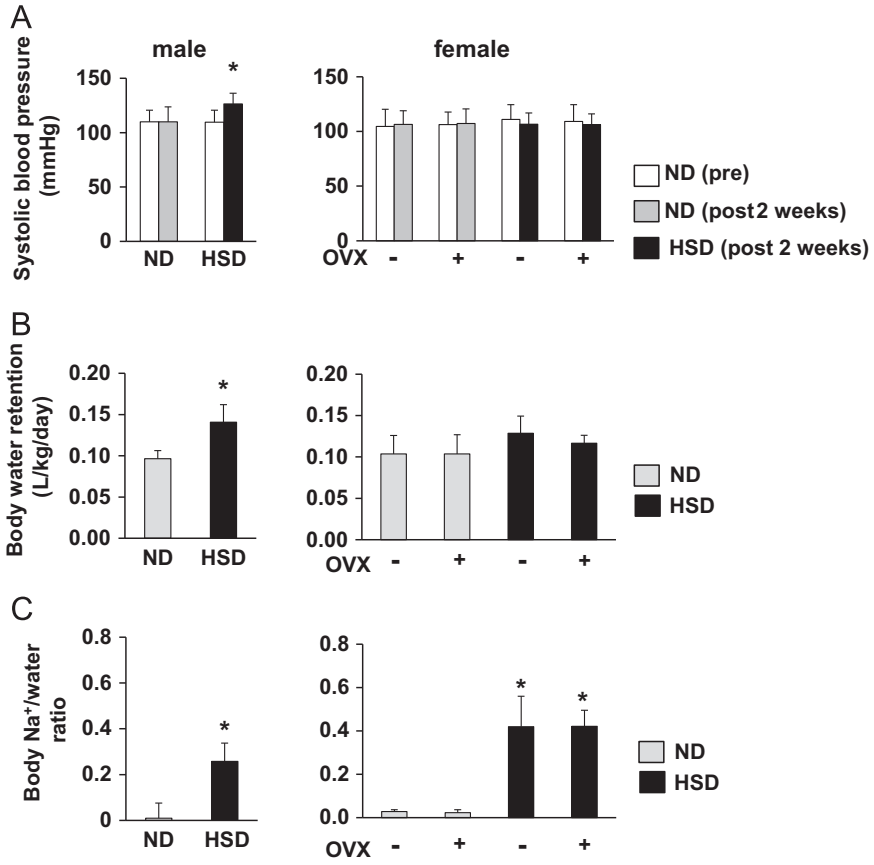

Fig. 1 – Effects of a high-salt diet (HSD, 8% NaCl) on the systolic blood pressure (SBP) (A), body water retention (B), and the body Na^+/water ratio (C) in male and female Wistar rats. Each datum represents the mean ± SD (each group, $n=16$). White bars in (A) represent the SBP in 9-week-old rats; colored bars the SBP in 11-week-old rats. *$p<0.05$ vs male ND by Student's t-test or OVX^-/ND by ANOVA followed by Scheffe's test. ND indicates a normal diet containing 0.3% NaCl; OVX, ovariectomy.