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COMMENT

Brain sodium exposure: inducing stroke onset independent of blood pressure elevation in stroke-prone spontaneously hypertensive rats

Keisuke Shinohara[1]

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Excessive dietary salt intake is strongly associated with the development of hypertension, which is a major risk factor for cardiovascular diseases including stroke. Furthermore, the clinical and pre-clinical studies have indicated that high salt intake can directly lead to adverse brain phenotypes such as central sympathetic activation [1, 2]. A high salt diet increases plasma or cerebrospinal fluid (CSF) NaCl concentrations by 2 to 6 mM in salt-sensitive human cohorts, as well as in various experimental models of salt-sensitive hypertension [2]. Importantly, chronic intracerebroventricular (ICV) infusion of hypertonic NaCl to elevate CSF Na^+ concentrations by 5 to 10 mM in rats produces a sympathetically mediated hypertension [3]. Therefore, the sympathoexcitation induced by the high salt diet might be attributed to the increase in CSF Na^+ concentration. However, whether brain sodium exposure induces stroke onset, has not been well elucidated.

The present study by Kajiwara et al. demonstrated that persistent brain exposure to high sodium by ICV infusion of NaCl induced stroke onset along with upregulation of cerebral microbleeds and oxidative stress in stroke-prone spontaneously hypertensive rats (SHRSP) compared to normotensive Wistar Kyoto rats (WKY) [4]. Specifically, saline solutions at concentrations of 0.9%, 2.7%, and 9% were intracerebroventricularly infused to WKY and SHRSP, with each treatment group defined as "WKY-0.9%," "SHRSP-0.9%," and so forth. Significant differences in stroke onset were observed between WKY-2.7% and SHRSP-2.7%, and between WKY-9% and SHRSP-9%. Although a direct comparison of stroke onset between SHRSP-2.7% and SHRSP-9% was not conducted, it appears to be more frequently observed in SHRSP-9% compared to SHRSP-2.7%. It would be of interest to examine this difference in stroke onset between sodium concentrations for ICV infusion within the SHRSP. In addition, it is noteworthy that the changes in systolic blood pressure induced by ICV infusion of saline were not significantly different between WKY and SHRSP within the same saline concentration. In fact, there appeared to be little change in systolic blood pressure induced by ICV saline infusion in either WKY or SHRSP (the data are shown in their Supplementary Fig. 2). As described in the previous paragraph, chronic ICV infusion of hypertonic NaCl with CSF Na^+ concentrations elevated by 5 to 10 mM induced hypertension in Dahl salt-sensitive rats [3]. This discrepancy in the blood pressure response to the ICV NaCl between the reports might be due to the difference in CSF Na^+ concentration, which was not shown in the study by Kajiwara et al., and/or the difference in rat strain. Besides, the serum NaCl concentration was significantly higher in SHRSP compared to WKY at each ICV NaCl concentration, whereas it was similar between WKY and SHRSP at baseline. The authors considered that the increased stroke onset mainly represented the effects of exposure to higher NaCl in the cerebral ventricle and the surrounding organs in the brain, rather than that in blood, given that the values of serum NaCl concentration in SHRSP were increased regardless of ICV NaCl concentration and also within normal range. Although the authors did not compare the serum NaCl concentration before and after high NaCl ICV infusion in WKY or SHRSP, the serum NaCl concentration appeared to be increased after the chronic NaCl ICV infusion in SHRSP, but not in WKY. This difference in changes in serum NaCl concentration may not be due to leakage of the blood-brain barrier (BBB) in SHRSP at 15 weeks of age, as previous studies have shown that the expression of intercellular adhesion molecule-1, an increase in which may

✉ Keisuke Shinohara
shinohara.keisuke.727@m.kyushu-u.ac.jp

[1] Department of Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

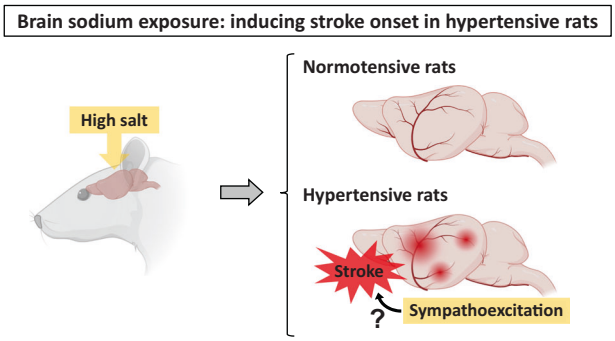

Fig. 1 Brain sodium exposure: inducing stroke onset in hypertensive rats. Sodium exposure in the brain induces stroke onset in stroke-prone spontaneously hypertensive rats. Further research is required to uncover its mechanisms, including the potential involvement of central sympathetic excitation

be associated with BBB dysfunction in the brain, is similar in SHRSP and WKY at 6 to 16 weeks of age, whereas it is increased in SHRSP compared with WKY at 18 to 23 weeks of age [5, 6]. Further studies are needed to elucidate the mechanisms by which high NaCl ICV infusion increases stroke onset and serum NaCl concentration.

Kajiwara et al. also demonstrated that activated microglia were increased in SHRSP-9% compared to SHRSP-0.9%: microglia are resident innate immune cells in the brain, and resting microglia are activated by various pathological events, including stroke. A recent study has shown that a high salt diet can induce microglial activation within the paraventricular nucleus of the hypothalamus, an important region for sympathetic control, contributing to sympathoexcitation and the development of hypertension [7]. Therefore, although Kajiwara et al. did not determine whether the activated microglia were a cause or a consequence of the stroke, the brain exposure to high sodium might, in itself, lead to microglial activation.

As described above, the link between high sodium intake/brain exposure to high sodium and sympathoexcitation has been well indicated. In addition, renal denervation, which can decrease sympathetic outflow [8], reduced stroke onset beyond the antihypertensive effect in SHRSP fed a high salt diet [9]. Further research is required to uncover the mechanisms responsible for the increased incidence of stroke in hypertensive rats following ICV infusion of high NaCl, including the potential involvement of central sympathetic excitation (Fig. 1).

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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