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COMMENTARY

The Two Faces of Estrogen in Experimental Hemorrhagic Stroke

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Hemorrhagic stroke, an umbrella term that encompasses intracerebral hemorrhage (ICH), intraventricular hemorrhage, and aneurysmal subarachnoid hemorrhage (aSAH), is a devastating disease and a leading cause of morbidity and mortality around the world. Studies investigating sex differences in humans after hemorrhagic stroke have shown that though men have an overall higher incidence of hemorrhagic stroke, women have a higher age-adjusted mortality rate [1]. Within hemorrhagic stroke, the aSAH cohort is unique in that women have been shown to have a higher incidence of aSAH, greater risk of delayed cerebral ischemia as well as higher morbidity and worsened brain injury [2]. Interestingly, the incidence of SAH also rises within the female population following menopause [2], indicating a possible age or hormone-related mechanism of aneurysm rupture. These differences have led to significant interest in the role of sex hormones, particularly estrogen, in outcomes after hemorrhagic stroke.

In ischemic stroke, it has been postulated that estrogen plays a protective role [3]. With respect to hemorrhagic stroke, multiple studies have shown that bilateral ovariectomy in a female rat intracranial aneurysm (IA) model leads to a higher incidence of SAH, an effect reduced by exogenous estrogen administration [4]. Interestingly, unruptured IA in female rats following bilateral ovariectomy was noted to be larger than in female animals without ovariectomy or males [4]. In ICH, estrogen has been shown to reduce brain edema and neuronal death and even lead to improved functional outcomes [5]. Indeed, female sex is associated with not only improved neurobehavioral recovery following ICH but also a concomitant change in gene and protein expression [6]. Taken together, the presence of estrogen has been shown to be beneficial in both aSAH and ICH.

However, recently, estrogen has been shown to potentially play a harmful role in the pathogenesis of hydrocephalus induced by intracerebroventricular thrombin, an important clot-derived pro-inflammatory factor. In particular, estrogen administration to male rats led to greater ventricular dilation and white matter injury via a neutrophil-mediated pathway following thrombin administration [7]. In the same study, female rats overall had a worsened outcome compared to their male counterparts following intracerebroventricular thrombin injection including higher mortality [7]. Furthermore, in an elastase model of SAH, female mice developed higher SAH rates than male mice [8]. When hydrocephalus, a downstream morbidity associated with aSAH, was evaluated after experimental SAH in the rat model, there was a significantly higher incidence in the female population [9]. SAH-induced brain injury may, in part, be due to cerebral venule thrombosis, which has been shown to have a greater occurrence in the female rats [10]. From this perspective, estrogen appears to be involved in a more harmful route of hemorrhagic stroke pathogenesis.

Regardless of the downstream effects of estrogen, there does appear to be some consensus that estrogen may exert its influence through inflammatory pathways. An increase in neutrophils was noted in an intracerebroventricular thrombin–induced hydrocephalus model in rats that were pre-treated with 17-β estradiol, and this was associated with worsened injury [7]. Female rats following bilateral ovariectomy had increased neutrophils and CD68-positive macrophages within unruptured aneurysms, similar to the phenotype usually seen in ruptured aneurysms [4]. Furthermore, these cellular changes appear to also be associated with changes in gene expression. In a study investigating differential gene expression between male and female mice

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following ICH, female mice had a unique increase in gene expression associated with pathways involving cytokine signaling and cellular immune response while both male and female mice had increased expression of pathways involving inflammation and apoptosis [6]. It should be noted that both the impact of sex on the inflammatory response and the role(s) of inflammation in brain injury may differ with the type of hemorrhagic stroke. This will add complexity to understanding the impact of sex and estrogen in hemorrhagic stroke.

Though, historically, endogenous estrogen has been seen as having a protective role, there exist more nuances to the mechanisms that underlie estrogen's role in hemorrhagic stroke, as is implied by the harmful effects seen in certain studies. While there has been significant research into the sexual dimorphism seen in ischemic brain injury [3], there continues to be a substantial gap in the current literature with respect to sex differences in hemorrhagic stroke. Overall, estrogen likely plays a dual role, potentially by modulating cytokine and inflammatory pathways, in outcomes following hemorrhagic stroke and further studies investigating the mechanism of estrogen's effects are necessary to gain a deeper understanding.

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Declarations

Ethical Approval All institutional and national guidelines for the care and use of laboratory animals were followed.

Conflict of Interest Sravanthi Koduri, Richard F. Keep, Ya Hua, Neeraj Chaudhary, Aditya S. Pandey, and Guohua Xi declare that they have no conflict of interest. Guohua Xi is Associate Editor of the *Translational Stroke Research.*

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