Sex, Steroids, and Stroke

Introduction

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Stroke remains a major source of mortality and disability, particularly among women. Stroke statistics consistently show a greater number of strokes occurring in women, more hospital discharges for stroke among women, and more women dying from stroke each year than men. American Stroke Association statistics show that 53% of the stroke fatalities each year are among women.1 Largely a function of the longer life-expectancy among women and the marked increasing stroke incidence with age, there may be other contributing factors to this stroke gender disparity. Most epidemiological studies have shown a greater age-specific stroke incidence for men compared with women. In Northern Manhattan, we observed an attenuation in the male–female stroke incidence for men compared with women. In Northern Manhattan, we observed an attenuation in the male–female stroke incidence for men compared with women. In Northern Manhattan, we observed an attenuation in the male–female stroke incidence for men compared with women. In Northern Manhattan, we observed an attenuation in the male–female stroke incidence for men compared with women.2

Many women have used hormone replacement therapy (HRT) in hopes of reducing cardiovascular disease and stroke, as well as perimenopausal symptoms. The basis for this practice arose from the early epidemiological observation that women’s stroke risk increases after the menopause and numerous observational studies that repeatedly associated HRT with reduced cardiovascular disease risk in women, including stroke. Furthermore, data from diverse animal and cell models of ischemic and/or hemorrhagic stroke indicate that estrogen is neuroprotective. At physiological doses, both chronic and acute estrogen pre-injury or postinjury treatment reduce histological brain damage.3 The concept that HRT is protective in cerebrovascular disease has recently been laid aside, based on the findings of 3 large, multicenter, randomized trials. Disappointing results emerged from these trials, including a lack of treatment benefit among stroke and transient ischemic attack survivors, women with cardiac disease, and the larger cohort of “healthy” postmenopausal women at risk for cardiac disease.4,5,6 The Womens’ Health Initiative (WHI) found an unexpected significantly deleterious effect of postmenopausal estrogens. Potential criticisms of these trials include the concern that for women who already had vascular disease, the initiation of chronic hormonal therapy poststroke or cardiac disease was too delayed to alter the disease prognosis. The WHI was limited by the fact that initiation of treatment was too long after menopause, the course of treatment was too long, the hormonal therapy was not physiological or administered noncyclically, the drugs used were equine formulations, and the dose selected was possibly incorrect.7 Despite these potential criticisms, these new data have provided grade A evidence to alter the recommendations regarding the use of postmenopausal estrogens for vascular disease treatment and prevention.8

The purposes of this Princeton session were: (1) to review basic science and clinical trial data for HRT (Brass9); (2) to describe sex differences in cell and animals models currently used in neuroprotection research at the bench (Hurn); (3) to evaluate novel forms of estrogen-like compounds as neuroprotectants (Simpkins10); and (4) to dissect the role of endogenous estrogens in migraine and young women with potential implications for stroke (Bousser11).

Several major issues emerged from the session presentation and its discussants. First, at least 2 forms of HRT were ineffective in randomized, prospective, clinical trials, ie, they failed to reduce stroke risk in women and have the potential to lead to increased risk of fatal stroke. It may be possible to block adverse vascular effects of hormone therapy (eg, antiplatelet therapy) or to selectively stimulate estrogen’s beneficial versus deleterious mechanisms in vascular disease. Second, preclinical data strongly demonstrate that estrogen, estrogen analogues, and selective estrogen receptor modulators reduce damage from experimental brain injury when administered during or after insult. Clinical trials to determine the therapeutic potential for these compounds for acute stroke treatment are currently lacking. Third, biological sex is an important variable in assessing mechanisms of ischemic cell death in vivo and in vitro. Preclinical studies could benefit from gender stratification, as is routine in clinical trials. Fourth, sex steroids impact the pathophysiology of neurovascular pathologies such as migraine and represent an important area of stroke research in young women. In aggregate, the hormone story appears to be far from over.

References


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