Review Article
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Menopause and ischemic stroke: a brief review

Abstract

Ischemic stroke is one of the leading causes of morbidity and mortality worldwide. Females are protected against stroke before the onset of menopause. Menopause results in increased incidence of stroke when compared to men. The mechanisms of these differences remain to be elucidated. Considering that there is a postmenopausal phenomenon and females in general, are living longer sex hormone-dependent mechanisms have been postulated to be the primary factors responsible for the premenopausal protection from stroke and later to be responsible for the higher incidence and increased the severity of stroke after menopause. Animal studies suggest that administration of estrogen and progesterone is neuroprotective and decreases the incidence of stroke. However, the real-world outcomes of hormone replacement therapy have failed to decrease the stroke risk. Despite the multifactorial nature of sex differences in stroke, here, we briefly discuss the pathophysiology of sex steroid hormones, the molecular mechanisms of estrogen receptor-dependent signaling pathways in stroke, and the potential factors that determine the discrepant effects of hormone replacement therapy in stroke.

Keywords: gender, stroke, epidemiology, hormones, receptors

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Abbreviations: VSMC, vascular smooth muscle cells; HRT, hormone replacement therapy; NO, nitric oxide; MCA, middle cerebral artery; HERS, heart and estrogen-progestin replacement study; WEST, women's estrogen for stroke trial; WHI, world health initiative trial; T-PA, tissue plasminogen activator; ER, estrogen receptor; KO, knock out; Na+/K+- ATPase, nka; ATP, adenosine triphosphate; K, potassium; OUA, ouabain; Ach, acetylcholine; BK, large conductance calcium-activated potassium; nNOS, neuronal nitric oxide synthase; eNOS, endothelial nitric oxide synthase

Introduction

Ischemic stroke morbidity is a major health cost burden globally. The incidence of stroke has slightly improved in some parts of the world; however, there remains minimal therapeutic targets preventing this debilitating disease. Risk factors for ischemic stroke include aging, hypertension, diabetes, obesity especially with increased waist-to-hip ratio, dyslipidemia, smoking, chronic kidney disease, and other cardiovascular diseases.[1] Epidemiological studies demonstrate that younger females are better protected from stroke than men.[2] This difference reverses as age advances in females and menopause ensues, resulting in higher incidence of stroke in females.[2] Menopause increases the stroke risk in females[3] as evident from Framingham epidemiological study.[4] Reports from animal studies also corroborate these findings.

Young and middle aged female rats have neuroprotective effects after a transient ischemic event and are reported to have less stroke volume.[5,6] There are fundamental differences in the estrogen receptor-dependent and independent signaling on the cerebral vasculature in females compared to males. Estrogen plays a role in vascular smooth muscle cells (VSMC), endothelial cells, neurons, and glial cells. It also affects lipids levels, inflammation, and the thrombotic function.[7] Other factors, including anatomic factors, genetic factors, cell death pathways, microRNAs, and stroke-related specific genes on the X and/or Y chromosomes, have been reported contribute to the differences in these outcomes.[8–11]

Discussion

Menopause and ischemic stroke

Menopause is defined as the absence of menstruation over a period of 12months. The average age of menopause is 51years (30-60years).[12] The incidence of hypertension and ischemic stroke is lower in 20-54 year old women when compared to similarly aged men and post-menopausal women.[13] There is almost twice the risk of ischemic stroke in women with natural menopause before 42years of age compared to those who developed menopause after 42 years of age[4] or between 50-54years.[14] Menstruation has positive and protective effects on cardiac and cerebral vascular system as well. Female rats and those receiving an oophorectomy plus hormone replacement therapy (HRT) rats have less myogenic tone and less pronounced myogenic response than males or females with oophorectomy but without HRT due to estrogen-induced elevated nitric oxide (NO) release and activity.[15] The concept of HRT was based on the beneficial effects seen in various experiments on animals.[15–17].

Sex hormones and ischemic stroke

Animal models have been designed to study sex differences in vivo and in vitro. Neurons derived from females have a higher tolerance to the toxic effects of dopamine compared to males[18] and *in vivo* studies using mice suggest that 24 after middle cerebral artery (MCA) stroke, young adult female mice have significantly smaller infarcts. Furthermore, surgical oophorectomy ameliorates this protective effect in stroke prone rats[19] and, estradiol replacement seems to have neuroprotective effects.[16,17] This evidence suggests that estradiol, a natural gonadotrophic hormone, provides a neuroprotective effect at normal physiological level in premenopausal females. Similarly, administration of progesterone resulted in reduced cortical infarct size in reproductive senescent female rats[20] as well in males rats.[21] The role of testosterone has been studied in both animals and humans. Castrated male rats showed no decrease in the size of stroke in a MCA occlusion model[22] whereas testosterone administration in non-castrated males

enhanced infarct size.[23] The results in rats are variable based on the dosage of testosterone administration[24,25] as are the differences in the outcome in human males. The risk and severity of stroke increase with lower testosterone levels[26] whereas increased testosterone level tends to increase the risk of stroke in young boys.[27]

Hormone replacement therapy and ischemic stroke

HRT is designed to reduce some of the post-menopausal symptoms such as heart disease after menopause. Depending on the formulation, it is comprised of either estrogen, progesterone, sometimes in combination with testosterone. It has been reported that there are additional benefits of HRT, such as boosting working memory.[28,29] However, HRT also comes with increased risks of breast cancer, endometrial cancer, and hypercoagulable state resulting in cerebral venous bleeding and infarction. Sex hormones are mainly metabolized in the liver. Thus any deviation of liver function or administration of drugs that are metabolized in the liver could result in metabolic derangement of HRT. Two large controlled trials from the Heart and Estrogen-Progestin Replacement Study (HERS)[30] and the Women's Estrogen for Stroke Trial (WEST)[31] did not show any significant improvements in the risk of stroke. However, the data from the World Health Initiative Trial (WHI), and meta-analysis of 28 other randomized trials[32] suggests 29% increased risk of stroke in healthy postmenopausal women on standard hormone therapy, whereas the risk of stroke increases considerably in women >60 years of age.[33]

In contrast, the results from animal studies universally suggest neuroprotective effects of HRT and decreased stroke risk.[16,17] This discrepancy is possibly multifactorial. Firstly, the majority of animals studied were young ovariectomized rodents rather than elderly postmenopausal animals. As aging is another one of the major risk factors for stroke, studies in young hormone deficient models might enhance the beneficial effects of HRT. Secondly, the enrollment criteria and the types of HRT were not uniform in the clinical trials. Thirdly, the population of patients enrolled in the clinical trials were different. Thus the genetic differences may contribute to the diversity of HRT outcomes and mask the significance. Finally, thrombotic mechanisms play a larger role in ischemic stroke, and estrogen has a prothrombogenic nature. The incidences of venous infarction[34] and ischemic stroke[34,35] are significantly higher in patients on HRT, especially when given to younger females. Experiments have shown that HRT decreases the fibrinolytic activity of tissue plasminogen activator (t-PA) in oophorectomized rats[36] whereas a randomized controlled study in healthy postmenopausal women shows a positive effect of HRT on the fibrinolytic system.[37] More validation of the usefulness of HRT is indeed required.

Molecular mechanisms of estrogen receptor-dependent signaling pathways in ischemic stroke

Despite our current understanding of the sex differences and HRT, there are several questions pertaining to the mechanism by which gonadotrophic hormones exert their effects remain unanswered. The role of estradiol on cerebral vascular disease is ambiguous based on the data from animal studies. Recent studies suggest that different subtypes of estrogen receptors (ER), including ERα and ERβ, play distinct roles in neuroprotection. In this regard, Dubal et al.,[38] demonstrated that deletion of ERα resulted in abolishment of neuroprotective effect, whereas preservation of neuroprotective effect was observed in ERβ knock out (KO) mice, suggesting that ERα could be the mechanistic link to the protective effect of estradiol.[38] Administration of physiological level of 17β-estradiol results in flow-medicated relaxation of human coronary arteries.[39] This vasodilatory effect likely comes from activation of Na+/K+- ATPase (NKA). NKA is an enzyme found in the plasma membrane of all animal cells. It acts by utilizing adenosine triphosphate (ATP) to induce sodium efflux and potassium (K) influx, which hyperpolarizes the cell membrane and reduces vascular constriction. Functional activity of NKA in the aorta of female rats is more sensitive to the vasodilatory effect of acetylcholine (Ach).[40]

Blocking NKA with Ouabain (OUA) increases vascular tone[41] moreover, reduces Ach-induced vascular relaxation in the aorta of both male and female rats, but less so in females suggesting lower NKA functional activity in females.[42] In another study, ovariectomized female rats do not exhibit differences in NKA function compared to the male counterparts, and chronic hormone replacement with 17β-estradiol restored the vasodilator effect of Ach on NKA.[43] Despite these findings, the effects of estradiol on NKA-dependent vascular relaxation in the central nervous system in postmenopausal females are not yet clear. Figure 1 depicts the different molecular pathways through which estrogen exerts the neuroprotective role. VSMCs tend to contract with the rise in perfusion pressure. This effect is countered by transient outward K current initiated by the large conductance calcium-activated potassium (BK) channels in VSMCs resulting in hyperpolarization of these cells.[44] 17β-estradiol activates BK channels directly.[45] BKβ1 is one of the downstream targets of sex hormones including 17β-estradiol and progesterone[46] and specifically activated by 17β-estradiol in the VSMCs;[46] increases neuronal nitric oxide synthase (nNOS) as well endothelial nitric oxide synthase (eNOS) expression; and releases NO in the endothelial cells, all of which promotes vasodilation.[47,48]

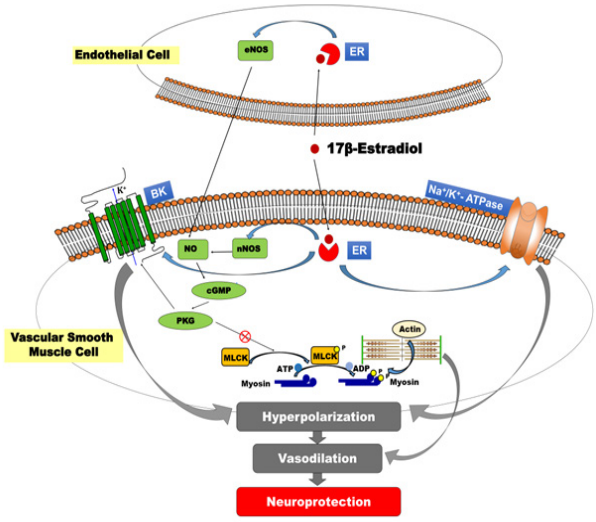

Figure 1 Neuroprotective role of 17β-estradiol. 17β-estradiol binds to intracellular estrogen receptor (ER). It activates endothelial nitric oxide synthase (eNOS) in the endothelium and neuronal nitric oxide synthase (nNOS) in the vascular smooth muscle cells (VSMC). Thus, resulting in enhanced release of nitric oxide (NO) and inhibits actin-myosin based vasoconstriction through activation of cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) pathway that inhibits myosin light chain (MLC) phosphorylation and activates the large conductance calcium-activated potassium channel (BK). 17β-estradiol binds to the ER to increase the expression and activity of Na+/K+-ATPase and has a direct effect to activate BK channels, both of which cause membrane hyperpolarization and vascular relaxation. The vasodilation effect plays a critical role in neuroprotection.

Conclusion

Epidemiologic studies reveal that age and sex differences play a role in the onset and outcomes of ischemic stroke. The levels of sex hormones, including estrogen and progesterone, are reduced in the elderly females. These changes alter estrogen receptor-dependent signaling pathways and increase the incidence and severity of stroke in the postmenopausal females. Animal studies demonstrate that postmenopausal HRT has beneficial effects on stroke, but the outcomes are not consistent in human studies due to multifactorial mechanisms. Further investigations are in need to elucidate the mechanisms and to develop novel therapeutic targets to reduce the risk of stroke in the postmenopausal females.

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Conflict of interest

The author declares no conflict of interest.

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