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Review

Window of opportunity: Estrogen as a treatment for ischemic stroke

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ABSTRACT

The neuroprotection research in the last 2 decades has witnessed a growing interest in the functions of estrogens as neuroprotectants against neurodegenerative diseases including stroke. The neuroprotective action of estrogens has been well demonstrated in both in vitro and in vivo models of ischemic stroke. However, the major conducted clinical trials so far have raised concern for the protective effect of estrogen replacement therapy in postmenopausal women. The discrepancy could be partly due to the mistranslation between the experimental stroke research and clinical trials. While predominant experimental studies tested the protective action of estrogens on ischemic stroke using acute treatment paradigm, the clinical trials have mainly focused on the effect of estrogen replacement therapy on the primary and secondary stroke prevention which has not been adequately addressed in the experimental stroke study. Although the major conducted clinical trials have indicated that estrogen replacement therapy has an adverse effect and raise concern for long term estrogen replacement therapy for stroke prevention, these are not appropriate for assessing the potential effects of acute estrogen treatment on stroke protection. The well established action of estrogen in the neurovascular unit and its potential interaction with recombinant tissue Plasminogen Activator (rtPA) makes it a candidate for the combined therapy with rtPA for the acute treatment of ischemic stroke. On the other hand, the "critical period" and newly emerged "biomarkers window" hypotheses have indicated that many clinical relevant factors have been underestimated in the experimental ischemic stroke research. The development and application of ischemic stroke models that replicate the clinical condition is essential for further evaluation of acute estrogen treatment on ischemic stroke which might provide critical information for future clinical trials.

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1. Basic research: estrogen as neuroprotection for ischemic stroke

Stroke is one of the leading causes of death and morbidity worldwide. Approximately, 1 in 6 people will have a stroke in their lifetime. In the United States, stroke currently ranks as the first leading cause of disability and the fourth leading cause of death. The epidemiologic data suggest that the decline in both stroke incidence and mortality reached a nadir in the early 1990s and is now rising because of the aging population (Stapf and Mohr, 2002). Stroke patients must not only survive the acute stages of infarction, but must then cope with significant mental, physical, and economic stresses associated with neurological impairment. Considering the cost in loss of life, physical and mental disability and subsequent loss of productivity, the need for effective therapeutic interventions is obvious.

Ischemic stroke is by far the most frequent type of stroke, accounting for over 80% of all stroke cases (Gillum, 2002). Two primary therapeutic approaches have been intensively studied for the treatment of acute cerebral ischemia: (i) vascular approach that targets re-opening occluded blood vessel and (ii) cellular approach to interfere with the pathophysiological cascades leading to ischemic damage (Schaller and Graf, 2004). The vascular approach is based on the fact that ischemic stroke is a cerebral vasculature event, initiated by occlusion of a cerebral artery and results in substantial brain tissue damage. Interruption of blood flow to the brain results in ischemia and deprives neurons and surrounding cells of crucial substrates. Unless the supply of these substrates can be restored, the cells in the region will ultimately die. Given the high energy demand and vulenrability of brain to ischemic damage, the vascular approach focuses on limitation of cerebral ischemia by early reperfusion after cerebral ischemia. The effort to develop effective vascular therapy for acute ischemic stroke achieved several important successes in 1990s. Based on the results from the National Institute of Neurological Disease and Stroke (NINDS) trial in 1995, intravenous recombinant tissue Plasminogen Activator (rtPA) is recommended for selected patients within 3 h of ischemic stroke onset (Wardlaw et al., 2003). The use of rtPA is now the only established stroke treatment for those patients presenting within 3 h of ischemic stroke onset. Beyond this time window, systemic rtPA does not appear to be as beneficial and increases the risk of serious side effects. Therefore, thrombolytic therapy has been severely limited by the need for hyper-acute administration with less than 5% of the potentially eligible patients receive the treatment (Zivin, 1999). Overall, rtPA and all other thrombolytic therapies, has less medical impact for the stroke patients.

In the last 2 decades, tremendous effort has been invested to develop new neuroprotective agents that aim to prevent the progression of ischemic cascades and reduce brain damage. Various neuroprotective strategies have been developed and tested for nearly all components of the ischemic cascades, including free radical scavengers, anti-excitotoxic agents, apoptosis inhibitors, anti-inflammatory agents, metal ion chelators, ion channel modulators, gene therapy and stem cells transplantation. The premise of neuroprotection has originally focused on the prevention of neuron from death. With recent research emphasizing ways to reduce tissue damage by both vascular and cellular mechanisms, the spotlight has been shifting towards the study of neurovascular interaction. The neurovascular unit provides a conceptual model comprised of cerebral endothelial cells, glia, and neurons, along with an extracellular matrix that maintains the integrity of brain tissues. This modular concept emphasizes the dynamics of vascular, cellular and matrix signaling in the brain (Del Zoppo, 2013; Lo et al., 2004). In addition, as a cerebral vascular event, ischemic stroke induces not only a complex array of pathogenic cellular cascades in brain parenchyma, but also impairment of autoregulation in brain vasculature at both acute and chronic stages (Cipolla et al., 1997; Cipolla and Curry, 2002; Jimenez-Altayo et al., 2007; Winters et al., 2012). Therefore, therapeutic intervention targets neurovascular unit and cerebral vasculatures might provide a more integrative framework that could guide the discovery of treatment for ischemic stroke (Zhang et al., 2012).

Estrogens were first described by Frank et al. (1925) as a component of the ovary needed for reproductive function. Later, estradiol was isolated and crystallized by Doisy et al. (1930). Among estrogens, 17β-estradiol is the most potent natured occurring estrogen. It is now clear that estrogens are pleiotropic hormones that functions beyond the scope of the reproductive system. The neuroprotection research in the last 2 decades has witnessed a growing interest in the functions of estrogens as neuroprotectants against neurodegenerative diseases, including stroke. The first experimental evidence to implicate possible role of endogenous female hormones as being neuroprotective against global cerebral ischemia-reperfusion injury showed that intact adult female rodents sustain less neuronal damage as compared to age-matched males (Hall et al., 1991). Later, estrogen was demonstrated a potent neuroprotectant in vitro (Bishop and Simpkins, 1994) and are very effective against ischemia-induced brain damage (Alkayed et al., 1998; Dubal et al., 1998; Simpkins et al., 1997). There is now abundant evidence for neuroprotection by estrogens both in vitro and in vivo (McCullough and Hurn, 2003). Importantly, the potency and efficacy of estrogens have