ABSTRACT

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Title: Influence of ovarian hormone deprivation length on the neuroprotective effects of genistein in stroke

BACKGROUND: Advancing age increases women’s susceptibility to stroke compared to men, especially after the menopausal transition. Among the reasons proposed for high stroke incidence in postmenopausal women is a significant decrease in estrogen (E2) concentration, a predominant female gonadal hormone. This stems from well-established evidence that E2 is neuroprotective in both animal and human studies under ischemic conditions. While E2 treatment can be beneficial, extended delays in its replacement can result in detrimental actions on the brain which contributes to widespread mistrust of menopausal hormone therapy. Interest in the beneficial effects of soy isoflavones has grown as a viable alternative for E2. However, results from clinical trials have been inconsistent as there seems to be no consensus on the benefits of soy isoflavones in menopausal women. Notwithstanding, there is evidence to suggest a time-dependent beneficial effect of soy isoflavones, even though there is no systematic assessment in preclinical studies to identify the window of opportunity for their proposed optimal benefits.

Hypothesis: After long-term hormone deprivation, the soy isoflavone genistein will maintain the ability to provide neuroprotection and mitigate detrimental biochemical changes in the brain following aging and the loss of endogenous E2 in an experimental stroke model.

METHODOLOGY: Young adult and proven retired breeder Sprague-Dawley rats were bilaterally ovariectomized and divided into 2 post-ovariectomized time points (2 and 12 weeks) and fed with isoflavone free (IF) diet. At the end of each time point, rats were continued on IF diet or switched to genistein diet. Two weeks later, rats underwent transient middle cerebral artery occlusion for 60 minutes. After stroke, rats were subjected to a series of behavioral tests including neurological function, cylinder test, rotarod, and the Morris Water Maze (MWM).

RESULTS: Our results demonstrated a significant effect of stroke, but not diet on the learning phase of the rotarod, reversal phase of the Morris Water Maze test and cylinder test. Comparison between the 2-week and 12-week young adults showed a significant interaction of stroke and length of ovarian hormone deprivation on the neurological deficit assessment. Comparison between the stroke subjects in the young adult and retired breeders showed a significant interaction of duration of ovarian hormone deprivation and the age of animal in the rotarod test and the MWM.

CONCLUSION: Genistein had little effect on the sensory and motor outcomes, it holds a promise in improving cognitive function post-stroke in the long term.