CHARPTER I

INTRODUCTION

Rational and significant of the study

Menopause is defined as the permanent cessation of menstruation resulting from the depletion of ovarian function (Josep and Mayo, 1999). It is marked by sudden change in the hormonal balance and estrogen hormone is decreased. It was suggested that the menopause may be a biological marker of aging (Snowdon, 1990). Thai women go through menopause when they are between 49 to 52 year old (Chompootweep, et al., 1993). Hill's study had predicted that the population of menopausal women throughout the word will be increased to 1.2 billion in 2030. (Hill, 1996).

Estrogen deprivation in menopausal women causes several physical changes including insomnia, hot flushes, vaginal atrophy and drying. These changes may along with osteoporosis and cardiovascular disease. Furthermore, menopausal women may experience behavioral changes such as mood disorders and cognitive dysfunction. Menopause associated with the cognitive changes which characterized by forgetfulness, loss of concentration and memory. Some study reported that menopausal women were much more likely to complain of memory loss than the women in the comparison group (Devi, et al., 2005). Furthermore evidence suggested that the deprivation of estrogen can increase risk for neurodegerative disease associated with learning and memory impairment, Alzheimer's disease (AD) (Gao, et al., 1998).

Brain-derived neurotrophic factor (BDNF) is a member of neurotrophin family. BDNF can mediate neuronal plasticity, differentiation, growth and survival in central and peripheral nervous system (Chao, 2003). There were evidences suggested that decrement of BDNF level associated with neurodegenerative disorder relating to learning and memory impairment (Lindsay, et al., 1991; Sohrabji and Lewis, 2006). Estrogen exerts its neuroprotective effect via the classical estrogen receptor subtypes (ERs), ER alpha (ERα) and ER beta (ERβ) which these receptors wildly distribute

throughout the hippocampus and cerebral cortex (Shughrue, et al., 1997). More evidences also indicated that estrogen affect on the BDNF expression in the hippocampus and cerebral cortex suggesting the crucial role of estrogen on the BDNF regulation (Spencer, et al., 2008; Luine and Frankfurt, 2013).

Estrogen replacement therapy (ERT) has demonstrated long-term benefits by improving unpleasant menopausal symptoms and protecting against menopause-related cognitive dysfunction; however, unopposed ERT is associated with serious side-effects such as endometrial cancer, breast cancer and venous thromboembolic events (Barrett-Connor and Grady, 1998).

Phytoestrogens are non-steroidal compounds obtained form plant and has estrogen-like properties. It was recognized that phytoestrogen can exert its effect similar to endogenous estrogen by binding with estrogen receptors (Rietjens, et al., 2012). Recently, phytoestrogens attracted interest as a potential alternative to the ERT.

Asparagus racemosus (AR) Willd or Shatavari, is a traditional medicine plant, locally known as Samsip in Thai (Boonsom, et al., 2012). It has phytoestrogenic properties and has been thought to be useful for female rejuvenation (Mayo, 1998). The major active compound presented in the AR root are steroidal saponins namely shatavarins (Hayes, et al., 2008). Thai traditional medicine has used the AR root to reduce menopausal symptoms. In addition, in Ayurvedic texts have recognized that AR can improve several diseases such as gastric ulcers, dyspepsia including has a galactogogue activity (Bopana and Saxena, 2007) and decreasing tumor (Rao, 1981). The neuroprotective properties of AR have been demonstrated by enhancing memory and protecting scopolamine-induced amnesia in rodents (Ojha, et al., 2010), reversing neuronal damage induced by kainic acid (KA) in mice (Parihar and Hemnani, 2004) and showing adaptogenic activity against different kinds of stressors in animals (Rege, et al., 1999). Although AR is well known for phytoestroginic and neuroprotective effects, the beneficial effects of AR on learning and memory impairment induced by ovariectomized (OVX) rat are unknown.

Purposes of the study

A general experiment objective

This experiment is designed to investigate the effects and mechanisms of AR root extract on learning and memory impairment induced by ovariectomy in rats.

Specific objectives

1. To investigate the effect of AR root extract on learning and memory in OVX rats.

2. To study the effect of AR extract on intact neuronal density in OVX rats.

3. To determine the effect of AR root extract on BDNF protein expression in OVX rats.

4. To evaluate the effect of AR root extract on ERs protein expression in OVX rats.

Scope of the study

This study used the adult sham-operated and ovariectomized female Wistar rats to investigate the effects of AR root extract on learning and memory. AR root extract at the dose of 100 and 1000 mg/kg B.W. were gavaged for ninety days before determining learning and memory abilities, serum estradiol levels, numbers of intact neuron as well as expression of BDNF and ERs protein. Learning and memory abilities were evaluated by using a novel object recognition (NOR) test. The serum estradiol levels were measured by using electrochemiluminescene immunoassay (ECLIA). The intact neuronal density in hippocampus and medial prefrontal cortex (mPFC) were examined by using a histological analysis. Finally, the expression of BDNF and ERs protein in the hippocampus and frontal cortex were evaluated by using a western blot analysis.

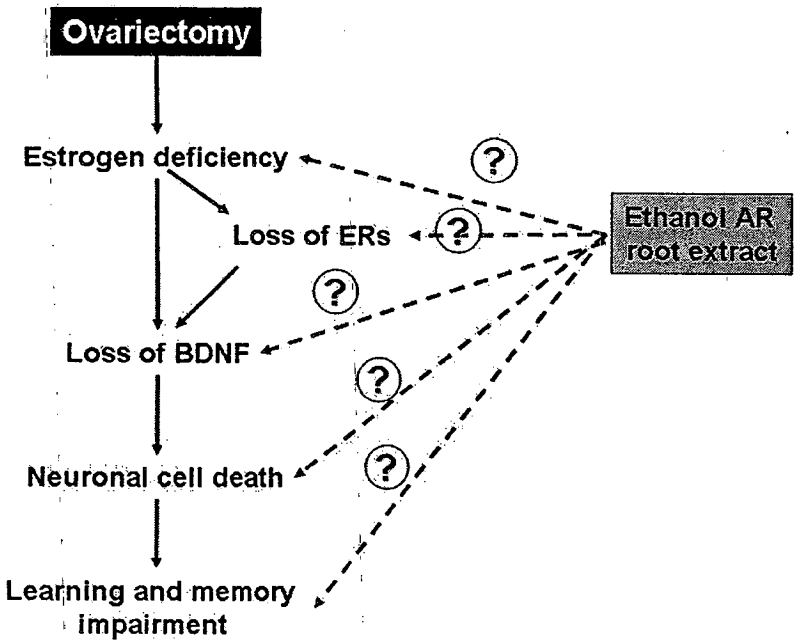

Figure 1 Conceptual research framework

Hypotheses

If AR has phytoestrogenic and/or neuroprotective effects, the animals receiving AR should improve their learning and memory associating with the increment of BDNF and ERs protein expression as well as number of intact neuronal cells.

Keywords

Asparagus racemosus, learning and memory, BDNF, ERs, ovariectomized rat

The anticipated outcomes of the study

The results from this study will show the effects and mechanisms of AR on learning and memory impairment induced by OVX. It may provide a basis for clinical studies as a new potential memory enhancing dietary supplement for menopausal women.