1. INTRODUCTION

Dementia has been recognized as a major public health issue that will grow in prominence as life expectancy increases. It has been proposed that estrogen (E2) deficiency in postmenopausal women may predispose older women to increased vulnerability of developing neurodegenerative diseases, such as Alzheimer’s disease (AD), and injury associated with cerebrovascular stroke. Indeed, some epidemiological data (1–3) indicate a higher incidence of dementia in women than in men, especially after the age of 85. Even though the gender differences in risk for dementia are generally shown for AD, not for vascular dementia (VaD), the longitudinal Bronx Aging Study reported that a history of myocardial infarction (MI) increased women’s risk to develop dementia fivefold but had no effect on dementia risk in men (3), suggesting the vascular effect on dementia in relationship to E2 status. In contrast, other studies report no gender differences in the age-adjusted incidence of dementia up to high age (4–6). In fact, the longer life expectancy in women than in men seemingly exposes women to higher risk of cognitive impairment in their late life.

During the past decades, we have become increasingly aware that E2 exerts several biological effects on tissues other than the reproductive system, first in maintaining bone integrity and much later in its effects on the immune, cardiovascular, and nervous systems (7–9). Osteoporosis, cerebrovascular disease (CVD), and dementia represent three of the most important causes of morbidity, lost independence, and death in older women. Ovarian production of E2 becomes negligible after menopause, and although serum E2 levels in postmenopausal women are highly variable, overall they decline markedly (7,10). There is biological plausibility that maintaining higher levels of E2 in postmenopausal women by means of E2 replacement therapy (ERT) could be protective against these diseases. On the basis of evidence mainly obtained from observational trials and biological studies, ERT had become one of the commonly recommended therapies with a presumed beneficial profile of cardiac protection, bone protection, and cognitive protection, as well as of well-being. However, studies from randomized controlled trials examining the risks and benefits of hormone therapy have produced conflicting results.

Beginning in 1998, results from a series of controlled clinical trials examining the effects of postmenopausal hormone therapy for the prevention of diseases have failed to show protection but instead demonstrated a slightly increased risk for cardiovascular events in women with established coronary disease (11) or in previously healthy women (12). The same findings were apparent for increased risk of ischemic stroke (13–15). In May 2002, the Women’s Health Initiative (WHI) (12) trial of daily combined therapy with estrogen plus progestin was terminated early because the risks (e.g., four more cases of coronary heart disease and stroke, nine more venous thromboembolisms,
and four more invasive breast cancers per 1000 women followed) outweighed the benefits (e.g., two fewer hip fractures and three fewer colorectal cancers). As a result, the striking discrepancies in studies have raised considerable confusion for both patients and health-care professionals regarding the use of hormone therapy. On the other hand, the discrepancies have also brought out questions about the validity of observational data, about methodological differences (e.g., confounding bias of "healthy user," adherence bias, and incomplete capture of early clinical events). Questions have also been raised about biologic issues, including formulation and dose of the hormone regimen and the characteristics of study population (e.g., time since menopause, endogenous E2 level, and stage of atherosclerosis) (16). Therefore, careful review of these studies and appropriate bridges between basic research findings with clinical relevance should not only enhance our understanding of the diverse actions of E2 but also facilitate the development of rational strategies that will promote overall health and cognitive function in older women.

In this chapter, clinical evidence from observational studies, which suggested a protective but inconsistent role for postmenopausal hormone therapy in cognitive function and dementia, is reviewed. In contrast, most recent controlled trials have failed to show the cognitive protection. On the other hand, there is a larger pool of biological evidence from in vivo animal models and in vitro cellular studies suggesting the protective role of E2 on cerebral vascular and brain function. This chapter focuses mainly on the role of E2 on cerebral blood flow (CBF) and neuromodulatory effects in response to ischemic insults. Some of underlying mechanisms involving the modulation of CBF and neuronal survival will also be addressed. In viewing growing evidence of inflammatory theory in the pathogenesis of neurodegenerative diseases, the biphasic and complex of tissue-specific effects of E2 on inflammation and the interactions between E2 and proinflammatory cytokines are discussed. In summary, current concerns and recommendations regarding postmenopausal hormone therapy for the prevention and treatment of cognitive impairment and questions that need to be answered in future studies are briefly discussed.

2. EFFECTS OF ESTROGEN ON COGNITION AND DEMENTIA

Most research on postmenopausal hormone therapy and cognition and dementia has studied and focused on AD as opposed to all-cause dementia, while a few distinguished VaD. Nevertheless, recent studies have suggested overlap between AD and VaD in pathogenesis, clinical symptoms, and treatment strategies. AD and VaD share certain vascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and hyperhomocystinemia, which are mainly modifiable risks and should be the focus for early interventional strategies. Here, the data available in VaD, as well as in AD, are reviewed.

2.1. Estrogen Deficiency, Cognition, and Dementia

Ovarian E2 production essentially ceases with the menopause. In postmenopausal women, serum estradiol concentrations are often lower than 20 pg/mL, and most of the estradiol is formed via extragonadal conversion of testosterone by the aromatase enzyme, which is expressed in many nonovarian tissues, including adipose tissues and the nervous system (7). Little is known about the regulation of E2 production in postmenopausal women. It is likely that body composition, polymorphisms in the genes coding for steroidogenic enzymes, and the expression and activity of aromatase influence the production of endogenous E2 in postmenopausal women, resulting in enormous interindividual variability (7,10). Several observational studies have demonstrated that the presence of particularly low endogenous E2 levels during post menopausal years may represent a risk factor for the development of dementia (17,18). For example, Yaffe et al. (18) reported that in a cohort of 425 women (65 yr or older) who had not received E2 therapy, women with higher endogenous serum levels of free and bioavailable estradiol at baseline, but not testosterone, were less likely to develop cognitive impairment 6 yr later. Although these findings suggest that higher concentrations of endog-