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Neurobiology of Aging 25 (2004) 159–166

NEUROBIOLOGY OF AGING

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Obesity enhances verbal memory in postmenopausal women with Down syndrome

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Received 19 August 2002; received in revised form 11 March 2003; accepted 25 March 2003

Abstract

Several lines of evidence suggest that the loss of estrogen after menopause may play a role in cognitive declines associated with Alzheimer's disease (AD). In postmenopausal women, the principal source of estrogen is estrone, which is influenced by body mass index (BMI). Increased BMI in postmenopausal women is associated with higher levels of serum estradiol and estrone. We hypothesized that obesity could have a beneficial effect on cognition with advancing age. We compared the performance of healthy nondemented obese and non-obese women with Down syndrome (DS) on a broad spectrum of cognitive tests. Estrone levels were 66.9% higher in obese than in non-obese postmenopausal women, and 136% higher in obese than in non-obese premenopausal women. Obese postmenopausal women performed significantly better than non-obese women on measures of verbal memory and on an omnibus test of neuropsychological function, but did not differ significantly in verbal fluency, language, praxis or visuospatial functioning. Among premenopausal women, there was no difference in cognitive function between obese and non-obese women. Our results support the hypothesis that higher endogenous estrogen levels after menopause are associated with better performance on verbal memory.

Keywords: Down syndrome; Menopause; Estrogen; Obesity; Body mass index; Cognitive function; Alzheimer's disease

1. Introduction

Estrogen has neuroprotective actions on the adult brain, and loss of estrogen following menopause may influence cognitive performance and risk for Alzheimer's disease (AD) in aging women [29]. Estrogen increases cholinergic activity [13,24,44], has antioxidant properties [4], and regulates the metabolism of the amyloid precursor protein (APP) to protect against the formation of neurotoxic β-amyloid [14,19,34,50].

Only a few studies have examined the relationship between endogenous estrogen levels and cognitive function in healthy postmenopausal women. Higher serum levels of total estrogens were associated with better performance on tests of verbal and visual memory [11,49], but were not associated with improved performance on an overall measure of mental status (MMSE) [35,51].

Estradiol is the principal estrogen in premenopausal women. After menopause, the primary estrogen is estrone, which is formed in adipose tissue, muscle, liver, bone marrow, brain, and fibroblasts from aromatization of circulating androstenedione [16,20]. Increased body mass index (BMI) in postmenopausal women is associated with higher levels of serum estradiol and estrone [10,31]. One study found that increased body weight in women with AD was correlated with better performance on two measures of global cognitive function [6]. In women with AD, weight loss associated with dementia onset or progression might lead to an association between low body weight and

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doi:10.1016/S0197-4580(03)00089-7

cognitive impairment. Determination of the effects of obesity in nondemented postmenopausal women may provide a better test of the beneficial effects of estrone on cognitive function.

In the current study, we examined the effect of obesity on cognition in healthy nondemented women with Down syndrome (DS). DS defined cytogenetically by trisomy 21, is the most common chromosomal disorder associated with mental retardation, occurring in approximately 1/1000 live births [18]. Women with DS experience early onset of menopause [9,39,40] and develop AD 10–20 years earlier than women in the general population [23]. The high risk for AD has been attributed to triplication and overexpression of the gene for β-APP, located on chromosome 21 [38], and virtually all adults with DS have the neuropathological changes associated with AD by 40 years of age [25,47]. Thus, it has been suggested that DS may serve as a model for the study of biological mechanisms involved in the pathogenesis of AD [22]. Because the interval between onset of menopause and the onset of AD is shorter than is typical in the general population, postmenopausal women with DS provide a unique cohort in which to study the relationship between loss of endogenous estrogen and cognitive decline related to AD. We hypothesized that obese postmenopausal women with DS would have higher levels of estrone and would perform better on tests of cognitive function than non-obese postmenopausal women. In contrast, we expected that there would be no difference in cognitive performance between obese and non-obese premenopausal women because the amount of estrone conversion in premenopausal women is small in comparison with estradiol secretion. Hence, the contribution of increased estrone to overall estrogen activity would be relatively low [54]. To test our hypothesis, we compared the performance of obese and non-obese women with DS on a broad spectrum of cognitive functions.

2. Methods

2.1. Subjects

Study participants were a community-based sample of 242 women with DS, aged 40–60 years, residing in the New York State. The study participants were ascertained through the statewide service system and recruited with the help of state and voluntary service provider agencies. Subjects were eligible to participate if they had a family member or correspondent who could provide informed consent, and subjects also signed a form acknowledging their willingness to participate. The participation rate among eligible subjects was 74.6%. Recruitment, informed consent, and study procedures were approved by the Institutional Review Boards of the New York State Institute for Basic Research in Developmental Disabilities and Columbia Presbyterian Medical Center and Columbia University Health Sciences.

2.2. Procedures

2.2.1. Ascertainment of menopausal status

Menopausal status, age of menopause, and use of hormonal replacement therapy/estrogen replacement therapy (HRT/ERT) were ascertained through menstrual chart and medical record review, and survey of primary care physicians and gynecologists. In many residential setting for women with DS, menstrual cycles are charted on a regular basis. For each cycle, the date, duration and severity of flow are noted. We used these menstrual charts, where available, to ascertain menopausal status and age at menopause, and we used final menstrual period (FMP) from the medical chart or physician surveys to ascertain age at menopause when menstrual charts were not available. The correlation between age at menopause ascertained from the different sources was substantial (0.77–0.99), suggesting that ascertainment of menopausal status and age at menopause was reliable. In keeping with convention, we classified age at natural menopause as the age at the last menstrual period preceding cessation of menses for 12 months, in the absence of known causes of amenorrhea (e.g. surgery). We also ascertained whether study participants were being treated with hormone replacement therapy and determined the type, age at onset and duration of the hormone therapy treatment.

2.2.2. Body mass index

BMI is a widely used measure of obesity, computed as weight in kilograms divided by height in square meters (kg/m^2). BMI was coded into three categories according to NIH clinical guidelines [32]: non-obese ($\leq 25.0\,kg/m^2$), overweight ($25.1–29.9\,kg/m^2$), and obese ($\geq 30.0\,kg/m^2$).

2.2.3. Assessment of cognitive function

Participants were evaluated with a neuropsychological battery to assess intellectual functions that are typically affected in AD and designed for a wide range of intellectual function. The tests included in the battery were based in part on recommendations by the AAMR-IASSMD Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability [7].

2.2.4. Verbal explicit memory

2.2.4.1. Selective Reminding Test. The Selective Reminding Test [8] is a standard diagnostic tool in the assessment of verbal explicit memory, which provides multiple measures that reflect the efficiency of some of the processing and storage components of memory underlying test performance [21]. We have modified the original structure of the Selective Reminding Test for use with adults with mental retardation, in order to avoid the floor effects that might be encountered if the instrument were utilized as originally constructed [17]. The test consisted of presenting a list of either eight familiar animals or eight familiar foods at a rate of one item per second. Immediately following the list