Review Article

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Antioxidant Enzymes in Acute Stroke Patients and Hemorrhagic Stroke

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Abstract

Some evidence suggests the neuroprotection of estrogen provided by the antioxidant activity of this compound. The main objective of this study was to determine the level of estradiol and its correlation with the activity of antioxidant enzymes, total antioxidant status and ferritin from ischemic stroke subjects. The study population consisted of 30 patients with acute ischemic stroke and 30 controls. There was no significant difference between estradiol in stroke and control group. The activity of superoxide dismutase and level of ferritin was higher in stroke compared with control group. Our results supported that endogenous estradiol of elderly men and women of stroke or control group has no antioxidant activity.

Introduction

Stroke is the third most common cause of death, particularly in the elderly. Ischemic stroke accounts for about 75% of all cases while hemorrhagic stroke is responsible for almost 15% of all strokes. Data on the link between endogenous estrogen and ischemic stroke in elderly men and women is limited and controversial. Before the menopause, women are relatively protected from ischemic stroke compared with men. This protection is most attributed to the action of estrogen but recent evidence has raised the possibility that sex-dependent differences in vascular oxidative stress may play a role [1]. In postmenopausal women and elderly men, the role of endogenous estrogen is not clear. Some studies have found that hyper estrogenemia is related to an elevated risk of coronary heart disease, although other studies have not.

Abbott et al. found elderly men with high level of serum estradiol have twofold excess risk of stroke compared with men whose estradiol levels were lower. Relationship between endogenous estradiol and antioxidant status of elderly men and women from stroke is less known. Some evidences suggest the neuroprotective of estrogen or estrogen derivatives provided by the antioxidant activity of this compound, but some studies are observed the antioxidant activity of estrogen, only with supraphysiologic dose of estrogen. Since oxidative stress is important mechanism involved in ischemic stroke [2], the activity of antioxidant enzymes may be an essential factor providing protection from neurological damage. Ferretti et al. found the higher level of lipid hydroperoxides in plasma from stroke patients compared with control group. The question whether endogenous estradiol can affect the activity of antioxidant enzyme or level of ferritin in the ischemic stroke has not been systematically addressed yet, although the activity of antioxidant enzyme and level of ferritin from stroke patients have been reported.

To the best of our knowledge, no information is available about correlation between endogenous estradiol and the activity of antioxidant enzymes from ischemic stroke patients. The main objective of this study was to determine the level of estradiol and its correlation with the activity of antioxidant enzymes and ferritin from ischemic stroke subjects [3].

Materials and Methods

Thirty patients older than 61 years with acute ischemic stroke admitted within 12 hours from the onset of symptoms to the emergency room of the Farshchian University Hospital, Hamadan, Iran, and were consecutively enrolled. On admission, demographic characteristics, a detailed history, and clinical information for stroke risk factors were recorded. Laboratory tests, chest radiography, and electrocardiography were performed in all patients. All patients were investigated to clarify etiologic factors for stroke. Computed tomography (CT) of the brain was performed in all patients. Subjects with hemorrhagic stroke, other neurological disease, patients with body temperature higher than 37.5°C, inflammatory process, diabetes mellitus, liver disease, and renal impairment, or taking iron or antioxidant vitamins or hormone replacement therapy during the months preceding the enrollment, were excluded from the study [4]. The severity of the neurological deficit was determind by Canadian Neurological Scale. Heparinized venous blood samples were taken and plasma was separated and stored at −70°C. Results from the patient group were compared with those obtained from 30 healthy subjects of comparable age and gender. None of the control subjects was undergoing pharmacological treatments. All subjects gave informed consent to participate in the study, according to the criteria of the Ethical Committee of Hamadan University of Medical Sciences.

Statistical Analysis

Results are expressed as means ± SD. Kolmogorov-Smirnov goodness of test was used for normality distribution of estradiol, total antioxidant status, superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, and ferritin. For comparing estradiol, total antioxidant status, superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, and ferritin between stroke and control groups, the Student's t test was used. In addition, correlation analyses were performed by means of the Pearson test. A value of $P < 0.05$ was considered significant [5].

Results

The study population consisted of 60 subjects: 30 patients with acute ischemic stroke admitted within 12 hours from onset (15 men and 15 women, aged 70.6±8.3 and 70.4±10.8 years, resp.) and 30 controls (15 men and 15 women, aged 68.5 ± 8.4 and 66.2 ± 7.6 years, resp.). The mean CNS score in stroke group was 6.3 ± 1.5.

Results of Total Subjects from Stroke and Control Group

The mean values of the estradiol, glutathione peroxidase, glutathione reductase, catalase, superoxide dismutase, total antioxidant status, and ferritin in the stroke and control groups are shown in (Table 1). There was no significant difference between estradiol in stroke and control group. The activity of superoxide dismutase and level of ferritin was higher in stroke compared with control group ($P<.05$) [6].

Results of Males and Females from Stroke and Control Group

The mean ± SD values of the estradiol, ferritin, and total antioxidant status, superoxide dismutase and glutathione peroxidase, glutathione reductase, and catalase of the males and females from stroke and control groups are shown in (Table 2). The correlation between estradiol and glutathione peroxidase, glutathione reductase, catalase, total antioxidant status and ferritin in males and females from stroke and control groups was not significant. There was inverse correlation between estradiol with superoxide dismutase in males of stroke patients. In addition, we found inverse correlation between estradiol with superoxide dismutase in females of stroke patients, but this difference was not significant (Table 3).

Table 1. The mean ± SD values of the estradiol, ferritin and total antioxidant status, superoxide dismutase and glutathione peroxidase, glutathione reductase and catalase of the stroke and control group.

Parameters	Stroke (*n* = 30)	Control (*n* = 30)
Estradiol (pg/mL)	63.8 ± 19.8	66.5 ± 9.6
Superoxide dismutase (U/mL)	174.53 ± 84.81*	123.94 ± 85.09
Glutathione peroxidase (U/L)	3993.40 ± 2696.19*	5775.27 ± 3348.77
Glutathione Reductase (U/g Hb)	2.78 ± 1.87	3.03 ± 1.93
Catalase (k/g Hb)	492.97 ± 115.39	456.11 ± 103.96
Total antioxidant status (mmol/L)	1.05 ± 0.25	1.12 ± 0.33
Ferritin (ng/mL)	101.92 ± 57**	66.54 ± 30.91

Table 2. The mean ± SD values of the estradiol, ferritin and total antioxidant status, superoxide dismutase and glutathione peroxidase, glutathione reductase and catalase of the males from stroke and control groups.

Parameter	Stroke (n = 15)	Control (n = 15)
Estradiol (pg/mL)	70 ± 19.6	64.5 ± 6.9
Superoxide dismutase (U/mL)	176.8 ± 89.6*	112.5 ± 62.6
Glutathione peroxidase (U/L)	4107.9 ± 3132.8	5791 ± 3913
Glutathione reductase (U/g Hb)	2.51 ± 1.98	3.7 ± 1.92
Catalase (k/g Hb)	504.8 ± 122.7	406.7 ± 123.4
Total antioxidant status (mmol/L)	1.05 ± 0.26	1.2 ± 0.34
Ferritin (ng/mL)	111.9 ± 60.5*	73 ± 35.3

Table 3. The mean ± SD values of the estradiol, ferritin and total antioxidant status, superoxide dismutase and glutathione peroxidase, glutathione reductase and catalase of the females from stroke and control groups.

Parameter	Stroke (n = 15)	Control (n = 15)
Estradiol (pg/mL)	55.4 ± 17.6	69 ± 12
Superoxide dismutase (U/mL)	171.4 ± 81.5	137 ± 106.5
Glutathione peroxidase (U/L)	3861.2 ± 2206.9	5758 ± 2759
Glutathione reductase (U/g Hb)	3.15 ± 1.72	2.2 ± 1.65
Catalase (k/g Hb)	476.9 ± 106.8	451.1 ± 82.3
Total antioxidant status† (mmol/L)	1.06 ± 0.25	1.02 ± 0.31
Ferritin† (ng/mL)	87.6 ± 50.7	58.4 ± 23.6

Discussion

In the present study, we have determined levels of estradiol, ferritin, total antioxidant status, and activity of antioxidant enzyme in ischemic stroke patients. Because of difficulties in determination of antioxidant enzymes in human cerebral tissue, the measurements were exclusively carried out in blood samples. Data on the relationship of endogenous estradiol and cerebrovascular disease in elderly men and women are limited. In our study, there was no difference between estradiol in stroke and control group. This finding suggests that the level of endogenous estradiol cannot prevent of occurrence of ischemic stroke [7]. Our results are consistent with Abbott et al. who reported high levels of serum estradiol that cannot protect elderly men against stroke. In the present study, ischemic stroke was associated with increased plasma activity of superoxide dismutase during the 12 hours after stroke. Because, after cerebral ischemia and particularly reperfusion, free-radical production is dramatically elevated, thus increased superoxide dismutase activity in stroke group may be a compensatory response to oxidative stress in stroke. The result is in agreement with Kocaturk et al. who have reported increased levels of superoxide dismutase in red blood cells after cerebrovascular accident.

In the present study, we did not observe positive correlation between estradiol and glutathione peroxidase, glutathione reductase, catalase, total antioxidant status, or ferritin in stroke or control group. In contrast, we found the negative correlation between estradiol and superoxide dismutase activity in males from stroke group. These data suggest a possible effect of estradiol reduction on increase of superoxide anion and induce oxidative stress in these patients. We suggested that increased of superoxide anion could induce increased superoxide dismutase activity in males of stroke patients which may be a compensatory response to oxidative stress in these patients [8]. However, we observed inverse correlation between estradiol and superoxide dismutase activity in females of stroke group, but the difference was not significant. The result is in agreement with Bertrand et al. who have reported increased level of serum total antioxidant status in postmenopausal women after estrogen replacement therapy. In the other hand, our data suggests that endogenous estradiol do not have antioxidant activity in stroke and control group with age greater than 61 years [9]. Some reports attributed an antioxidant activity to estradiol but the antioxidant activity is observed only with supraphysiologic concentration of this hormone. In the current report, evidence suggests that neuroprotective effects of endogenous estradiol against stroke are not related to antioxidant effect of this compound. It is not clear whether estrogen therapy has potential effect on oxidative stress in stroke patients. It seems that more studies are needed to make clear the role of estrogen therapy on antioxidant status of ischemic stroke patients. In this study, we observed higher level of ferritin in stroke compared with control group. Recent clinical studies have been proposed that high plasma levels of ferritin might be associated with increased risk of ischemic stroke. Ferritin might induce oxidative stress via being a

donor of free iron that is a source of hydroxyl radicals [10]. There are some limitations in the present study. First, small number of stroke and control individuals. Second, in this study, we did not determine correlations between estradiol and reactive oxygen species or some metabolite of lipid and DNA peroxidation such as malondialdehyde and 8- oxoguanine in ischemic stroke group. Thus, further studies are needed to clarify the role of endogenous estradiol on antioxidant status of ischemic stroke patients.

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