African Journal of Biotechnology Vol. 9(5), pp. 732-734, 1 February, 2010
Available online at http://www.academicjournals.org/AJB
ISSN 1684–5315 © 2010 Academic Journals

Short Communication

Decreased endogenous progesterone and ratio of progesterone to estrogen in stroke ischemia

Nasrin Sheikh[1], Heidar Tavilani[1]* and Aliakbar Rezaie[2]

[1]Department of Biochemistry, School of Medicine Hamadan University of Medical Sciences, Hamadan, Iran.
[2]Department of Neurology, School of Medicine Hamadan University of Medical Sciences, Hamadan, Iran.

Accepted 22 December, 2009

Progesterone and estrogen are two steroid hormones whose exposure may decrease the risk and delay the onset of ischemic stroke. The main objective of this study was to determine the plasma level of progesterone, estrogen and ratio of progesterone/estrogen in ischemic stroke patients. The plasma levels of progesterone, estrogen and ratio of progesterone/estrogen in 30 patients (15 men and 15 women) with acute ischemic stroke was determined within 12 h of the onset of the attack as well as in 30 control subjects (15 men and 15 women) of comparable age. There were significant differences between the progesterone and ratio of progesterone/estrogen of stroke and control group (p = 0.022 and p = 0.001, respectively). Compared with control, stroke patients had lower levels of progesterone and ratio of progesterone/estrogen. There were not significant differences between levels of estradiol in stroke and control groups. The results showed ischemic stroke is accompanied by reduction of progesterone and ratio of progesterone/estradiol. These reductions might be involved in the decreased protection of brain to ischemic injury.

Key words: Estradiol, ischemic stroke, progesterone.

INTRODUCTION

Progesterone and estrogen are gonadal hormones that are present in the blood circulation of both males and females and whose exposure may decrease the risk and delay the onset of ischemic stroke (Singh, 2006; Stein and Hoffman, 2003). Neuroprotective effects against cerebral ischemia of both hormones have been shown (Stein, 2008; Alonso et al., 2006). Study on animal and tissue culture models suggest that the loss of both estrogens and progestins makes the brain more vulnerable to acute insults and chronic neurodegenerative diseases (Simpkins et al., 2005). A number of studies have investigated the roles of progesterone and estrogen in stroke in humans, focusing primarily on incidence, sex, age of first stroke and outcome (Roof and Hall, 2000; Abbott et al., 2007; Stein, 2007). But, most attention has focused only on progesterone or estrogen alone and only a few instances have concomitantly evaluated the role of progesterone and estrogen from stroke patients (Toung et al., 2004; Alkeyed et al., 2000). The questions are whether plasma level of progesterone and estrogen or ratio of progesterone to estrogen is different in ischemia stroke patients compare to controls. To the best of the present knowledge, no information is available about change of progesterone to estrogen ratio from ischemia stroke patients. The main objective of this study was to determine the plasma level of progesterone, estrogen and ratio of progesterone/estrogen in ischemic stroke patients.

MATERIALS AND METHODS

Thirty patients older than 61 years with acute ischemic stroke admitted within 12 h from the onset of symptoms to the emergency room of the Sina University Hospital, Hamadan, Iran, were consecutively enrolled. On admission, demographic characteristics, detailed history and clinical information for stroke risk factors were recorded. Laboratory tests (blood cell count, biochemical studies including lipid profiles and serum electrolytes, urinalysis), 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

*Corresponding author. E-mail: tavilani@gmail.com. Tel: +98 811 8276295. Fax: +98 811 8276299.

Table 1. Plasma levels (mean ± SD) of progesterone, estradiol and ratio of progesterone/estradiol of stroke and control groups.

Parameters	Stroke (n = 30)	Control (n = 30)	P value
Progesterone (nmol/l)	4.1 ± 2	5.08 ± 1	0.022
Estradiol(nmol/l)	0.23 ± 0.07	0.24 ± 0.03	0.54
Progesterone/Estradiol ratio	16 ± 7.7	21.6 ± 2.9	0.001

and patients with body temperature higher than 37.5 °C, inflammatory process, diabetes mellitus, liver disease and renal impairment were excluded from the study. None of the stroke subjects was undergoing hormone replacement treatments. The inclusion criteria for controls were age ≥ 59 years, outpatient healthy subjects and nonsmokers. The exclusion criteria for controls were inflamemation, infection, presence of neurological dysfunction and history of myocardial infarction. The severity of stroke at admission was measured by Canadian Neurological Scale (CNS) (Cote et al., 1989). 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. Written informed consents were obtained from all participants or their relatives, according to the criteria of the Ethical Committee of Hamadan University of Medical Sciences.

Progesterone and estradiol assay

Plasma progesterone and 17-β estradiol was measured using a quantitative competitive immunoassay kit (DRG Instruments Company, Germany). The level of progesterone and 17-β estradiol is expressed as nmol/L.

Statistics

Results were expressed as means ± SD. Kolmogorov-Smirnov goodness of test was used for normality distribution of progesterone, estradiol and progesterone/estradiol ratio and CNS score. Student's t test was used to detect differences of progesterone, estradiol, progesterone/estradiol ratio and CNS score between males and females from stroke and control groups. A value of $p < 0.05$ was considered significant.

RESULTS

The study population consisted of 60 subjects: 30 patients with acute ischemic stroke admitted within 12 h from onset (15 men and 15 women, aged 70.6 ± 8.3 and 70.4 ±10.8 years, respectively) and 30 controls (15 men and 15 women, aged 68.5 ± 8.4 and 66.2 ± 7.6 years, respectively). The mean CNS score in all patients of stroke group was 6.35 ± 1.5. The mean CNS score in men and women of stroke group was 6.8 ± 1.1 and 5.6 ± 1.35, respectively, and the difference was significant ($p < 0.05$). Progesterone and estradiol was assayed in duplicate for each plasma sample. The mean values of the progesterone and estradiol and progesterone/estradiol ratio in the stroke and control groups are shown in Table 1. There were significant differences between level of progesterone and progesterone/estradiol ratio in stroke compared to control group ($p = 0.022$ and $p = 0.001$, respectively). The mean values of the progesterone and estradiol and progesterone/estradiol ratio in the males and females of stroke and control groups are shown in Table 1. There were not significant differences between the level of progesterone, estradiol and progesterone/estradiol ratio in males and females in stroke or control group.

DISCUSSION

In the present study, the plasma levels of progesterone, estradiol and progesterone/estradiol ratio in the patients with ischemic stroke and healthy subjects were determined. The study showed that there were significant differences in levels of progesterone and progesterone/estradiol ratio in stroke patients compared to control group. Some information has been obtained regarding the mechanism underlying progesterone's neuroprotective effects (Singh, 2006; Stein et and Hoffman, 2003; Simpkins et al., 2005). The neuroprotection was provided by protecting the blood-brain barrier, reduction of cerebral edema, reduction of inflammatory cytokines, limiting cellular necrosis and apoptosis and antioxidant effects (Singh, 2006; Stein, 2008; Simpkins et al., 2005; Alkeyed et al., 2000; Vaisi-Raygani et al., 2009; Kharrazi et al., 2008).

The findings showed that endogenous progesterone was decreased in stroke compared to control group. The decrease of progesterone in stroke group may be partly due to reduction of synthesis or increase of metabolism to other compounds. A number of researchers studied the progesterone effect on reduction of the conesquences of cerebral ischemia. Administration of progesterone resulted in a significantly smaller cortical infarction volume, less weight loss and better neuralgic outcome (Stein, 2008; Alkeyed et al., 2000). Jiang et al. (1996) showed that the administration of progesterone before middle cerebral artery occlusion caused a reduction in cerebral infarction. In addition, administration of progesterone after the ischemic event can protect brain against injury (Morali et al., 2005; Kumon et al., 2000). Although in most studies, the effect of exogenous progesterone has been studied and less is known about the relationship of stroke with endogenous progesterone.

In the present study, the ratio of progesterone/estradiol was lower in stroke compared to control group. Some

evidence suggested that the greater neuroprotection attributed in females compared with males is likely due to effects of circulating progesterone and estrogen(Stein and Hoffman, 2003; Simpkins et al., 2005; Roof and Hall, 2000; Toung et al., 2004). In fact, exogenous administration of both hormones has been shown to improve outcome after cerebral ischemia in experimental models (Roof and Hall, 2000). It is not clear whether endogenous progesterone and estrogen insert neuroprotection effect in company with the other or not. In the most research, progesterone or estrogen is studied alone and the possible link of these hormones against stroke was not noticed. Since, in stroke group, the greater p-value for ratio of progesterone/estradiol ($p = 0.001$) compared to progesterone ($p = 0.022$) was found, this finding suggest that the ratio of progesterone/estradiol is a more important factor compared to progesterone or estradiol alone.

In conclusion, the present results showed ischemic stroke is accompanied by reduction of progesterone and ratio of progesterone/estradiol. These reductions might involve decreased in the protection of brain to ischemic injury.

ACKNOWLEDGMENT

This research was supported by Hamadan University of Medical Sciences.

REFERENCES

Abbott RD, Launer LJ, Rodriguez BL, Ross GW, Wilson PW, Masaki KH, Strozyk D, Curb JD, Yano K, Popper JS, Petrovitch H (2007). Serum estradiol and risk of stroke in elderly men. Neurology, 68: 563-568.

Alkeyed NJ, Murphy SJ, Traystman RJ, Hurn PD, Miller VM (2000). Neuroprotective effects of female gonadal steroids in reproductively senescent female rats. Stroke, 31: 161-168.

Alonso de Lecinana M, Egido JA (2006). Estrogens as neuroprotectants against ischemic stroke. Cerebrovasc. Dis. 21: 48-53.

Cote R, Battista RN, Wolfson C, Boucher J, Adam J, Hachinski V (1989). The Canadian Neurological Scale: validation and reliability assessment. Neurology, 39: 638-643.

Jiang N, Chopp M, Stein D, Feit H (1996). Progesterone is neuroprotective after transient middle cerebral artery occlusion in male rats. Brain. Res. 735: 101-107.

Kharrazi H, Vaisi-Raygani A, Rahimi Z, Tavilani H, Aminian M, Pourmotabbed T (2008). Association between enzymatic and non-enzymatic antioxidant defense mechanism with apolipoprotein E genotypes in Alzheimer disease. Clin. Biochem. 41: 932-936.

Kumon Y, Kim SC, Tompkins P, Stevens A, Sakaki S, Loftus CM (2000). Neuroprotective effect of postischemic administration of progesterone in spont-aneously hypertensive rats with focal cerebral ischemia. J. Neurosurg. 92: 848-52.

Morali G, Letechipía-Vallejo G, López-Loeza E, Montes P, Hernández-Morales L, Cervantes M (2005). Post-ischemic administration of progesterone in rats exerts neuroprotective effects on the hippocampus. Neurosci. Lett. 382: 286-290.

Roof RL, Hall ED (2000). Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J. Neurotrauma. 17: 367-388.

Simpkins JW, Yang SH, Wen Y, Singh M (2005). Estrogens, progestins, menopause and neurodegeneration: basic and clinical studies. Cell. Mol. Life. Sci. 62: 271-280.

Singh M (2006). Progesterone-induced neuroprotection. Endocrine, 29: 271-274.

Stein DG (2008). Progesterone exerts neuroprotective effects after brain injury. Brain. Res. Rev. 57: 386-397.

Stein DG (2007). Sex differences in brain damage and recovery of function: experimental and clinical findings. Prog. Brain. Res.161: 339-351.

Stein DG, Hoffman SW (2003). Estrogen and progesterone as neuroprotective agents in the treatment of acute brain injuries. Pediatr. Rehabil. 6: 13-22.

Stein DG, Wright DW, Kellermann AL (2008). Does progesterone have neuroprotective properties? Ann. Emerg. Med. 51: 164-172.

Toung TJ, Chen TY, Littleton-Kearney MT, Hurn PD, Murphy SJ (2004). Effects of combined estrogen and progesterone on brain infarction in reproductively senescent female rats. J. Cereb. Blood. Flow. Metab. 24: 1160-1166.

Vaisi-Raygani A, Tavilani H, Zahrai M, Rahimi Z, Sheikh N, Aminian M, Pourmotabbed T (2009). Serum butyrylcholinesterase activity and phenotype associations with lipid profile in stroke patients. Clin. Biochem. 42: 210-214.