OXIDATIVE INJURY AND ANTIOXIDANT VITAMINS E AND C IN SCHIZOPHRENIA

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ABSTRACT

Susceptibility of Schizophrenic patients to lipid peroxidation relative to healthy control subjects was investigated by measuring the malondialdehyde (MDA) levels in plasma. The main finding was that Schizophrenic patients were more susceptible than control subjects to oxidative damage as evident from increased MDA levels in plasma. Antioxidant levels are also depleted in Schizophrenic patients when compared to normal subjects as evident from decreased levels of vitamins E and C in the plasma. Impaired antioxidant defense and increased lipid peroxidation suggests that treatment with antioxidants (Vitamin E, Vitamin C, beta carotene) at the initial stages of illness may prevent further oxidative injury and deterioration of associated neurological deficits in Schizophrenia.

KEY WORDS

Lipid peroxidation, antioxidant vitamins E & C, Schizophrenia.

INTRODUCTION

Lipid peroxidation is a crucial step in the pathogenesis of several diseases. It is a process generated naturally in small amounts in the body, mainly by the effect of several reactive oxygen species. It can also be generated by the action of several phagocytes. These reactive oxygen species readily attack the polyunsaturated fatty acids of the membrane, initiating a self-propagating chain reaction. The destruction of membrane lipids and the end products of such lipid peroxidation are especially dangerous for the viability of cells, even tissues (1, 2).

The oxidative damage caused by the free radicals is thought to be a basic mechanism underlying many diverse pathological conditions. These free radicals are capable of damaging cellular components and accumulating evidence suggests that they may contribute to various disease entities such as diabetes, atherosclerosis, central nervous system (CNS) disorders, renal diseases and carcinogenesis (3, 4, 5).

Enzymatic (Catalase, Super oxide dismutase) and nonenzymatic (Vitamins A, E and C) natural antioxidant defense mechanisms exist. However these mechanisms may be overcome causing lipid peroxidation to take place. Since lipid peroxidation is a self propagating chain reaction, the initial oxidation of only a few lipid molecules can result in significant tissue damage.

A serum lipid peroxide level, therefore measures the overall potential for oxygen free radical pathology, the risk for degenerative processes and the need for compensatory antioxidant supplementation. High serum lipid peroxide levels indicate excessive oxygen free radical lipid peroxidation.

Brain has large lipid content of myelin sheaths and high rate of brain oxidative metabolism. Therefore brain is a more susceptible target of free radical damage. The recent hypothesis that free radicals may be involved in the pathogenesis of certain CNS diseases has gained increasing popularity in recent years (6, 7, 8, 9).

Although some studies are carried out in various types of carcinomas and brain tumors, very few reports are available on the role of antioxidants and lipid peroxidation in Schizophrenic patients. Schizophrenia is a mental illness characterized by specific psychological symptoms and leading in the majority of cases, to a disorganization of the personality of the patient. The symptoms interfere

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with the patient's thinking emotions, conation and motor behavior and with each in a characteristic way. The disorganization of personality often results in chronic invalidism and life long hospitalization in spite of the absence of gross physical signs or symptoms (10, 11).

There is increasing evidence that oxidative injury contributes to pathophysiology of Schizophrenia indicated by the increased lipid peroxidation products in plasma and CSF and altered levels of both enzymatic and nonenzymatic antioxidants in chronic and drug naive first episode Schizophrenic patients (12).

This study evaluates the association between lipid peroxidation and antioxidant vitamins E and C in Schizophrenic patients.

MATERIALS AND METHODS

All the chemicals used were of analytical grade available in India.

14 chronic patients admitted at the Dept. of Psychiatry, K M C Hospital, Attavar, Mangalore, with the diagnosis of Schizophrenia were selected between the age group of 29 to 68 years. The results were compared with those of 18 age and sex matched normal subjects who comprised the Control group. The diagnostic criteria of Schizophrenia are as follows: Clinically characteristic symptoms like delusions, hallucinations and thought disorders, suspicious, social withdrawal, loss of ego boundaries, loose thought associations, rapid shifting from topic to topic, autistic absorption in inner thoughts, impaired concentration and depersonalization. All patients considered for the study were prescribed treatment with 5 mg Trifluoperazine (once daily, bedtime dose) or 20 mg Penfluridol (half tablet, once in a week) or 100 mg Chlorpromazine (two daily, bedtime dose). The patients were on treatment for 2-6 months.

Random blood samples were collected in EDTA bottles from Schizophrenic patients and normal healthy individuals. Blood collected in EDTA bottles was centrifuged at 3000g for 10 minutes. Plasma was collected taking care to avoid hemolysis and used for the estimation of lipid peroxidation, vitamins E and C.

LIPID PEROXIDATION

The plasma lipid peroxidation (Thiobarbituric acid

reactive substances-TBARS) was studied by the method proposed by Satoh (13). Values were expressed as nanomoles of MDA formed per deciliter plasma taking the molar absorption of MDA as 1.5×10^{-5} (14).

Vitamin E was measured using the method of Bieri *et al* (15).

Vitamin C

Ascorbic acid in plasma was measured by using the property of its oxidation into dehydroascorbic acid. (16)

Statistical analysis

The data obtained was analyzed using Mann Whitney test.

RESULTS AND DISCUSSION

The plasma MDA levels estimated in Schizophrenic patients were significantly high when compared to controls. This indicates lipid peroxidation is significantly increased in Schizophrenic patients ($p = 0.0249$). The plasma vitamin E concentration decreased significantly ($p = 0.0455$) in Schizophrenic patients compared to normal subjects. Plasma vitamin C concentration in Schizophrenic patients decreased significantly ($p < 0.0005$) compared to control subjects. (Table 1)

These results indicate that there is free radical mediated CNS neuronal dysfunction involved in the pathophysiology of Schizophrenia, and the antioxidant defense is impaired. Free radicals like super oxide anion, hydroxyl ion and nitric oxide etc. can cause cell injury when antioxidant defense is impaired. Alpha Tocopherol (Vitamin E) can act as antioxidant to prevent the formation of peroxides and toxic compounds that cause cell lipid peroxidation (17, 18).

Free radicals cause cell injury when they are generated in excess or the antioxidant defense is impaired (19). Both of these processes seem to be affected in Schizophrenia. Evidence of excessive oxyradical generation is premised on the assumption that there is increased catecholamine turnover, though there is little direct evidence to support such a view. Another theory suggests production of free radicals from metabolism of dopamine, norepinephrine and antipsychotic drugs (20). Antipsychotic agents cause an increase in the metabolic turnover of catecholamines. Free radicals

produced during monoamine oxidation of catecholamines cause cellular damage, producing lipid peroxides that in turn change the membrane characteristics and thereby affect neurotransmission. These processes deplete the natural supply of free radical scavengers. This may explain the delayed development and irreparable damage.

The brain is more vulnerable to oxyradical-mediated injury because its membranes are preferentially enriched in oxyradical sensitive polyunsaturated fatty acids (PUFA) and damaged adult neurons cannot be replaced (21). In addition to their pathological role, oxyradicals have critical physiological functions in neuronal development, differentiation and signal transduction all of which may be altered in schizophrenia.

In the present study we have found that there is

increase in lipid peroxidation and decreased antioxidants (Vitamins E and C) in schizophrenic patients, which may cause oxyradical-mediated injury of CNS in Schizophrenia. Adjunctive treatment with antioxidants (Vitamins E and C) at the initial stages of illness may prevent further oxidative injury and thereby ameliorate and prevent further possible deterioration of associated neurological and behavioral deficits in schizophrenia.

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TABLE 1
COMPARISON OF PLASMA LEVELS OF MDA, VITAMIN E AND VITAMIN C IN
SCHIZOPHRENIC PATIENTS AND CONTROLS (Mean $\pm$ S.D.)

GROUP	MDA (n mol/L)	VITAMIN E (mg/L)	VITAMIN C (mg/L)
Control (n = 18)	196.57 $\pm$ 73.35 (56.41 – 282.05)	7.5611 $\pm$ 2.5203 (5.2 – 13.2)	0.8078 $\pm$ 0.51965 (0.263 – 2.04)
Schizophrenic Patients (n = 14)	271.36 $\pm$ 100.86 (87.17 – 374.35)	6.108 $\pm$ 2.779 (2.01 – 10.89)	0.2904 $\pm$ 0.196 (0.056 – 0.639)
p – value	0.0249	0.0455	0.0005

n = number of samples, S. D. = Standard Deviation

p - value calculated by Mann Whitney test.

The figures in the parentheses indicate the range.

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