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Evaluation of Plasma Total Antioxidant Response and Total Peroxides in Different Symptoms of Schizophrenia Patients

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Abstract: This study aims to measure Total Antioxidant Capacity (TAC) and Total Peroxides (TP) in schizophrenia patients with positive, negative and cognitive symptoms using Ferric Reducing Activity of Plasma (FRAP) and evaluate its relations with oxidative stress. We measured the plasma total antioxidant potential and total peroxides in 60 schizophrenia patients and in 60 well-matched non-schizophrenic control subjects. The association between the total antioxidative-oxidative potential and the symptoms, severity of schizophrenia were studied. Total antioxidant capacity/total peroxide of the clinical samples was measured using latest spectrophotometric measurement method. Results showed that plasma TAC was found to be lower in patients with schizophrenia than those of controls. On the contrary, the patients had high total plasma peroxide levels. Oxidative Stress Index (OSI) values of the patients were significantly higher than those of controls ($p<0.001$). Plasma TAC of each schizophrenia symptoms were significantly lower than healthy controls ($p<0.01$ for patients with negative and cognitive symptoms and $p<0.001$ for patients with positive symptoms). When intragroup comparisons were performed, patients with positive symptoms had significantly very low plasma TAC levels ($p<0.001$) compared to other negative ($p<0.01$) and cognitive subtypes ($p<0.01$). Plasma TAC in schizophrenia patients was significantly and inversely correlated with symptom severity. This study indicates that schizophrenia is associated with increased oxidative stress, depleted antioxidant status in schizophrenia subjects and supplementation with more antioxidative supplements could be considered in treatment.

Key words: Schizophrenia, symptoms, total antioxidant capacity, total peroxide, oxidative stress index

INTRODUCTION

There is abundant evidence that free radicals are involved in membrane pathology in the central nervous system and may play a role in neuropsychiatric disorders including schizophrenia (Akyol *et al*., 2004). Schizophrenia is a serious hereditary disorder of the brain resulting from abnormalities that arise early in life and disrupt normal development of the brain. The chemical nature of schizophrenic brain is still not completely understood. The brain and nervous system are particularly prone to free radical damage, since the membrane lipids are very rich in polyunsaturated fatty acids and certain areas of human brain are very rich in iron, which plays an essential role in generating free radical species (Dusica and Vesna, 2002).

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Free radicals adversely modify biologically active molecules and whole cells and are implicated in a variety of neurodegenerative diseases including schizophrenia and ageing (Glód *et al*., 2000; Tabner *et al*., 2002). The ability of a tissue or fluid to buffer the effects of reactive oxygen species is called total antioxidant capacity. Changes in the concentration of free radicals and indirectly, the total antioxidant capacity of blood plasma occur for two main reasons. First, patients are treated with L-dopa and other catecholamines which are antioxidants and the hyper metabolism caused by characteristic schizophrenia increases the concentration of free radicals. It is widely believed that these modifications and free radicals are eliminated from the body by their interaction with antioxidants (Obata, 2002). Blood contains many antioxidant molecules that prevent and/or inhibit harmful free radical reactions (Young and Woodside, 2001). Since antioxidative effects of antioxidant components of plasma are additive, the measurement of total antioxidant capacity reflects the antioxidative status of plasma. We evaluated the total antioxidative status of plasma by FRAP assay as proposed by (Benzie and Strain, 1996, 1999). Total antioxidant capacity parameter summarizes overall activity of non-enzymic antioxidants and antioxidant enzymes. It provides information about antioxidant types and their concentration without exact qualitative differentiation.

Hydrogen peroxide and other derivatives of peroxides, produced physiologically in organisms and occurring in higher concentrations in some pathological conditions, diffuse into plasma. Here, antioxidant components of plasma overwhelm them and they are consumed (Koracevic *et al*., 2001). In the present study, we evaluated the total oxidative status of plasma by measuring total peroxide level.

It has been reported that the antioxidant system is impaired and also increased oxidative stress may be present in patients suffering with schizophrenia (Hui-chun *et al*., 2006). It has been reported that plasma lipid hydro peroxide levels are increased and total antioxidant capacity decreased in schizophrenia patients (Toescu, 2002). However, the nature of this mechanism is not yet known and in the present state of knowledge there has been no report involving the total oxidative/antioxidative status of plasma in the schizophrenia patients with different symptoms and the significance of their levels remain unclear. So in our study, we aimed to measure the level of TAC values in plasma samples from schizophrenia patients to evaluate their antioxidant status using a novel automated method. As a reciprocal measure, the Total Peroxide (TP) levels of the same plasma samples were also measured (Harma *et al*., 2005; Yeni *et al*., 2005). The ratio of the plasma TP level to the TAR level was regarded as the Oxidative Stress Index (OSI). The above assays were performed in schizophrenia patients with different symptoms and its correlation with its severity of schizophrenia.

MATERIALS AND METHODS

Subjects

The study was conducted in the Postgraduate and Research Department of Biochemistry, Dr. N.G.P. Arts and Science College, Coimbatore during the month of September 2004 to June 2007. A total of 60 schizophrenic patients of age group 18-65 years of both sexes from good socio-economic background were selected from Udhayam Mananala kaapagam, a mental Health care center, Coimbatore, Tamilnadu, India. The patients were divided into three groups: (1) schizophrenics with positive symptoms, n = 20, (2) schizophrenics with negative symptoms, n = 20 and (3) schizophrenics with cognitive symptoms, n = 20. Positive And Negative Symptoms Score (PANSS) was done and all patients met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000) for schizophrenia.

The positive symptoms of schizophrenic patients ranging in average age from 19 to 58 (mean±SD; 29.8±11.5) years; the negative symptoms of schizophrenic patients 20 to 59 (32.7±12.3) years and the cognitive symptoms of schizophrenic patients 22 to 51 (36.9±8.9) years.

Control

Sixty age and gender matched healthy normal control subjects with no individual and family history of mental illness were recruited to participate in this study. They included 30 males and 30 females. Their ages ranged from 15 to 65 years with mean age (28.9±14.1) years. Both patients and controls were recruited during the same period from Coimbatore district. Study subjects were currently within normal ranges in their routine blood, urine and feces tests, electrocardiograph and radiographs; disorders associated with heart, brain, lung, liver, kidney and other pivotal organs were excluded.

The design and the layout of this project was carried out with the approval the Chairman, Kovai Medical Center and Hospitals and due permission was obtained from the board of institutional review Committee of the Kongu mananala Arakkattalai, before the start of the work. Informed and written consent was obtained from all subjects prior to examination.

Determination of Plasma Total Antioxidant/Total Peroxide Potential

Measurement of Total Antioxidant Capacity (TAC)

The TAC of the plasma was measured using a novel, automated, spectrophotometric measurement method developed by Benzie and Strain (Benzie and Strain, 1996, 1999) and modified by Erel (2004a). In this method, hydroxyl radical, which is the most potent biological radical, is produced. In the assay, ferrous ion solution, which is present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequential produced radicals, such as brown-colored dianisidine radical cation, produced by the hydroxyl radical, are also potent radicals. In this assay, the antioxidative effect of the sample against the potent free radicals' reactions, which is initiated by the produced hydroxyl radical, is measured. The assay results are expressed as mmol Trolox equivalent L^{-1} (Benzie and Strain, 1996, 1999; Toescu *et al*., 2002). The precision of this assay is excellent. Accurate measurements of TAC can be obtained in as little as 10 min, making this assay eminently suitable for the clinical biochemistry laboratory (Harma *et al*., 2005).

Measurement of Total Peroxide Concentration (TP)

Total Peroxide (TP) concentrations were determined using the FOX2 method (Miyazawa, 1989) with minor modifications (Harma *et al*., 2005; Yeni *et al*., 2005). The FOX2 test system is based on oxidation of ferrous ion to ferric ion by various types of peroxides contained within the plasma samples, to produce a colored ferric-xylenol orange complex whose absorbency can be measured. The FOX2 reagent was prepared by dissolving ammonium ferrous sulfate (9.8 mg) in 250 mM H_2SO_4 (10 mL), to give a final concentration of 250 μM ferrous ion in acid. This solution was then added to 90 mL of HPLC-grade methanol containing 79.2 mg butylated hydroxytoluene (BHT). Finally, 7.6 mg xylenol orange was added with stirring to make the final working reagent (250 μM ammonium ferrous sulfate, 100 μM xylenol orange, 25 mM H_2SO_4 and 4 mM BHT in 90% vol/vol methanol in a final volume of 100 mL).

The blank reagent contained all the components of the solutions except ferrous sulfate. Aliquots (200 μL) of plasma were mixed with 1800 μL FOX2 reagent. After incubation at room temperature for 30 min the vials were centrifuged at 12,000 g for 10 min. Absorbency of the supernatant was then determined as a function of the absorbency difference between test and blank tubes, using a solution of H_2O_2 as standard. The coefficient of variation for individual plasma samples was less than 5%.

Oxidative Stress Index (OSI)

The percent ratio of the TP to the TAC gave the Oxidative Stress Index (OSI), an indicator of the degree of oxidative stress ((Harma *et al*., 2005; Yeni *et al*., 2005; Yanik *et al*., 2004). To perform the calculation, the result unit of TAC, mmol Trolox equivalent L^{-1}, was converted to μmol equivalent L^{-1} and the OSI value was calculated by the formula:

$$OSI = [(TP, \mu mol\ L^{-1})/(TAC, \mu mol\ Trolox\ equivalent\ L^{-1}) \times 100]$$

Statistical Analysis

Results were expressed as mean±standard deviation. Differences were considered significant at a probability level of $p<0.05$. Obtained results were evaluated by repeated measurement variance analysis. Correlation analysis was done between TP, TAC and OSI.

RESULTS

A total of 60 schizophrenia patients and 60 non-schizophrenia subjects were recruited. Table 1 shows the total antioxidant capacity of schizophrenia subjects with positive, negative and cognitive symptoms.

TAC level was 0.976±0.44, 1.36±0.52, 1.42±0.43 and 1.99±0.47 mmol Trolox eq. L^{-1} in the positive, negative, cognitive symptoms of schizophrenia groups and in the control group, respectively; TP level was 19.63±1.39, 17.21±1.67, 18.021±1.32 and 13.95±1.79 μmol H_2O_2 L^{-1} in the same study groups and in the control group, respectively; OSI values were 1.95±1.89, 1.34±2.98, 1.16±0.87 and 0.61±1.45 arbitrary Units in the positive, negative and cognitive group and in the control group, respectively. The comparison between the schizophrenia group and the control group revealed that the level of TAR was significantly lower and TP and OSI levels were significantly higher in all the study groups ($p<0.01$), but these changes were statistically more significant in the study group with positive symptoms ($p<0.001$).

The values of TAR in chronic patients(0.92±0.43 mmol Trolox eq. L^{-1}) were significantly lower compared to acute patients (1.23±0.47 mmol Trolox eq. L^{-1}) ($p<0.01$). The mean (±SD) levels of TP and OSI in acute patients were significantly lower (16.13±1.47 μmol H_2O_2 L^{-1} and 1.41±2.12) compared to chronic patients (18.78±1.49 μmol H_2O_2 L^{-1} and 2.34±0.72) at $p<0.01$ (Table 2).

Correlation analysis were performed and are shown in Fig. 1. Figure 1a shows the correlation between TP and TAC of type: 1 (Schizophrenic with positive Symptoms). Here the total peroxides formed and total antioxidant capacity are par with each other indicating that peroxides produced are scavenged by the antioxidant systems. In the case of type 2 (Schizophrenic with Negative symptoms) (Fig. 1b), there was a linear increase in total peroxides and total antioxidant capacity ($r = 0.945$). But in type 3 (schizophrenics with cognitive symptoms) (Fig. 1c) a negative correlation was obtained ($r = -0.763$) indicating the increase in oxidative stress Similar observations were seen while relating the total antioxidant capacity and oxidative stress (Fig. 1e-h).

Table 1: Circulatory levels of a. TAC, TP and OSI in schizophrenia patients with different symptoms and healthy control groups

Parameters	Type 1	Type 2	Type 3	Control
TAC-FRAP (mmol Trolox eq. L^{-1})	0.976±0.44$^{a\ ab,c}$	1.36±0.52^{a}	1.420±0.43^{a}	1.99±0.47
Total peroxides TP (μmol H_2O_2 L^{-1})	19.630±1.39$^{a\ ab,c}$	17.21±1.67^{a}	18.021±1.32^{a}	13.95±1.79
Oxidative stress index	1.950±1.89$^{a\ ab,c}$	1.34±2.98^{ad}	1.160±0.87^{a}	0.61±1.45

Type 1: Schizophrenic with positive Symptoms; Type 2: Schizophrenic with Negative symptoms; Type 3: Schizophrenic with cognitive symptoms, a b c and d $p<0.01$; a* $p<0.001$, a: Statistical significance compared to control group; b: Statistical difference between positive and negative group; c: Statistical difference between positive and cognitive group; d: Statistical difference between negative and cognitive group

Table 2: Plasma levels of TAR, TP and OSI in acute and chronic Schizophrenia patients (Values are mean±SD)

Parameters	Acute schizophrenics	Chronic schizophrenics
TAC-FRAP (mmol Trolox eq. L^{-1})	1.23±0.47	0.92±0.43*
Total peroxides TP (μmol H_2O_2 L^{-1})	16.13±1.47	18.78±1.49*
Oxidative sress index	1.41±2.12	2.34±0.72*

Statistical comparison was done between acute and chronic Schizophrenics *: $p<0.001$

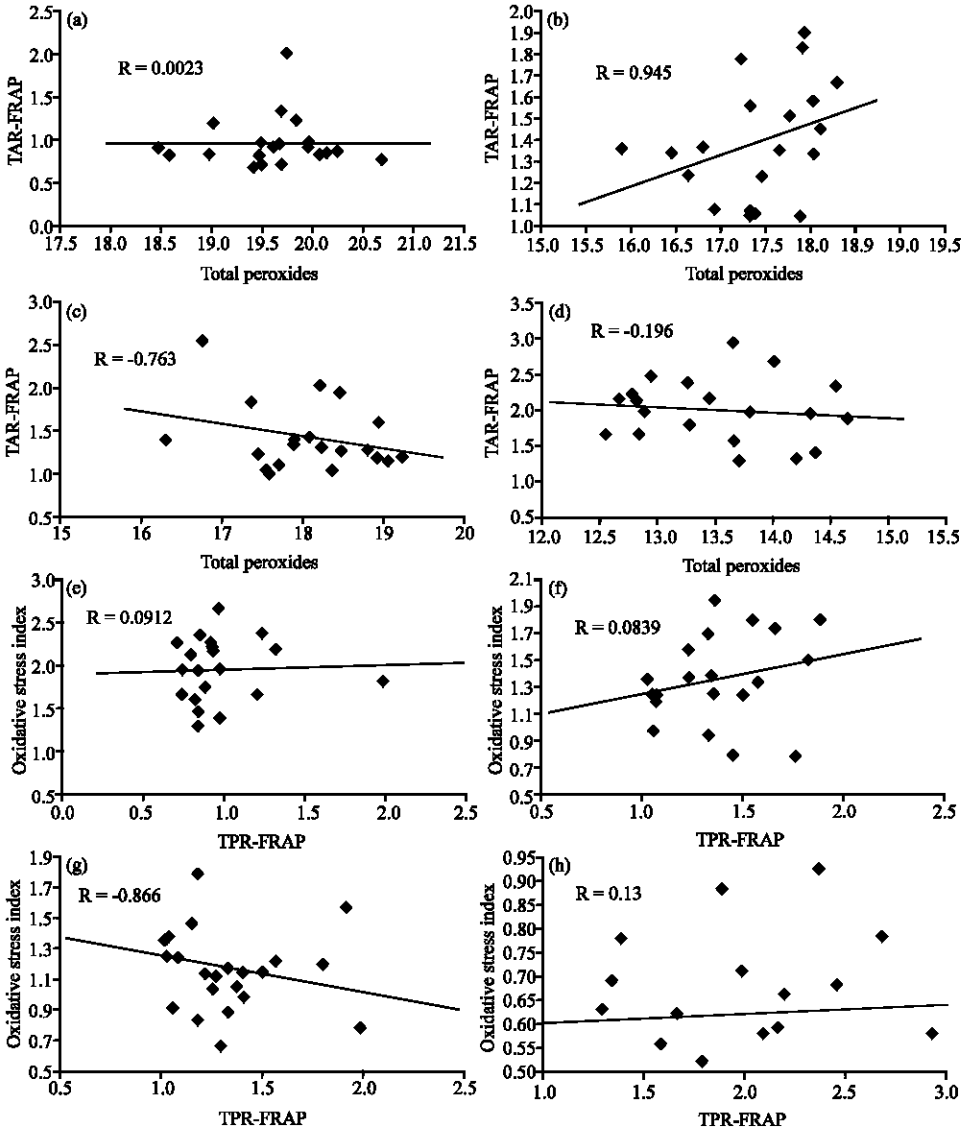

Fig. 1: (a) Correlation between TP and TAC (type 1), (b) Correlation between TP and TAC (type 2), (c) Correlation between TP and TAC (type 3), (d) Correlation between TP and TAC control), (e) Correlation between TAC and OSI (type 1), (f) Correlation between TAC and OSI (type 2), (g) Correlation between TAC and OSI (type 3) and (h) correlation between TAC and OSI (control)

DISCUSSION

There is a large amount of convincing data demonstrating that Reactive Oxygen Species (ROS) are involved in initiation and development of many different forms of schizophrenia. The levels of oxidants and antioxidants in schizophrenia have been evaluated. However, measurements of Total Antioxidant Capacity (TAC) and total peroxides in schizophrenia patients having different symptoms

and their severity (acute and chronic phases of the disease) based abnormalities were not evaluated up to date. Therefore, the objectives of this study were to investigate plasma TAC-TP levels in schizophrenia with different symptoms. Our results indicates that the oxidative/ antioxidative balance shifted towards oxidative status, namely increased oxidative stress was present in patients with schizophrenia compared with healthy control subjects.

It was indicated that ROS and other oxidants could be also formed in the normal physiological process (Onder and Gurer, 2001). Increased ROS, in turn, enhance LPO products, thus, lead to tissue injury (Yazici *et al*., 2004; Onder and Gurer, 2001). H_2O_2 and other derivatives of peroxides increase in some conditions, diffuse into plasma. Here, antioxidant components of plasma overwhelm them and they are simultaneously consumed (Young and Woodside, 2001; Murat *et al*., 2002).

When TP is measured, it means that the sum of many peroxides like protein peroxide, lipid peroxide and H_2O_2 are measured (Abuja and Albertini, 2001). Although it is known that H_2O_2 and lipid peroxides increase in schizophrenia (Herken *et al*., 2001; Dusica and Vesna, 2002; Hui-chun *et al*., 2006; Dadheech *et al*., 2006; Surapareni, 2007), oxidative stress has not been evaluated through TP-TAC in schizophrenia. It has been reported by Ustundag *et al*. (2002) that TAC level decreases in schizophrenia patients and decreased plasma total antioxidant levels may be related to the progression of illness. It was shown in the present study that TAC level also decreased in schizophrenia patients compared with control subjects.

It was observed in our study, among patients with different symptoms, there was a statistically more significant decrease was found in the level of TAC in patients with positive symptoms ($p<0.001$). It was clear from the results that there was no significant difference in the levels of TAC and TP between negative and cognitive symptomatic people, though the levels differed from the control subjects. Possible reasons for this increase in TP might be the inevitable increase in lipid peroxides and ROS including H_2O_2 in schizophrenia. Many antioxidant molecules found in blood prevent or inhibit the harmful effects of free radicals (Young and Woodside, 2001). Whenever there is a decrease in antioxidants and/or an increase in oxidants, oxidant/antioxidant balance is impaired in favor of oxidants and this is known as oxidative stress (Abuja and Albertini, 2001; Ghiselli *et al*., 2000). It is known that oxidative stress is responsible for tissue injury in many diseases and contributes to the development of schizophrenia (Granot and Kohen, 2004). Antioxidant activity indicates the antioxidant characteristics of only one antioxidant, whereas TAC represents the total antioxidant characteristics of all antioxidants found in the plasma. TAR and Total Antioxidant Status (TAS) are used synonymously with TAC (Ghiselli *et al*., 2000). It is doubtlessly more advantageous to evaluate TAR, instead of individual antioxidant activities. Since it has been reported that TAR, a new measurement method developed by Erel, correlated with data obtained by other measurement methods and has had some extra advantages (Erel, 2004a, b), we followed this method in our study.

Ustundag *et al*. (2002) have reported a decrease in TAR level in schizophrenia patients. Similarly, TAR level was found low in the study groups in the present study. A negative correlation ($r = -0.763$) existed between TP and TAC in Type 3 and also in control($r = -0.196$) but not to the level as seen in Type 3. Type 3 also showed a negative correlation in TAR and OSI ($r = -0.866$). The other groups Type 1, 2 and control a positive correlation was obtained when correlations between TP and TAC and TAC and OSI were done indicating that the subjects were able to mitigate the oxidative stress developed. The increase in TP and OSI levels and the tion between these increases and TAC level in the present study suggest that a possible cause of the decrease in TAC level may be increased oxidative stress. The decrease in TAR is not possible to attribute to only one of the individual antioxidants. Therefore, the decrease in TAC must have resulted from the decrease in combination of many antioxidants. In the light of these data, a possible reason for the decrease in TAR in schizophrenia may

be the decrease in other antioxidants, like enzymic and non enzymic antioxidants. As TAR is a fairly good representative of antioxidant capacity and TP and OSI are representatives of oxidant capacity, decreased TAC and/or increased TP levels indicate oxidative stress (Erel, 2004a, b; Ghiselli *et al*., 2000; Yanik *et al*., 2004). In the present study, there was a significant decrease in TAR level and an increase in TP and OSI levels in the study groups. Based on our results, it is necessary to consider the fact that increased ROS and LPO products as a result of neurodegeneration can be responsible for the impairment in oxidant/antioxidant balance, the increase in ROS and LPO products and the decrease in antioxidant capacity are expected to be more marked in the positive group ($p<0.001$) in comparison to the negative and cognitive groups ($p<0.01$). By our study, it is also possible that the oxidant/antioxidant balance is impaired at the onset of the disease and continues In conclusion, TAR is an appropriate measurement method demonstrating oxidant/antioxidant balance. Oxidant/antioxidant balance seems to be impaired at all stages and symptoms of schizophrenia. Further the impairment was more pronounced in patients with positive symptoms, elderly patients and male schizophrenia patients. In future, wethink that this argument should be confirmed by controlled, multi-centered, prospective studies, which shall include large case series and employ reviewed disease activity criteria.

TAC of plasma was significantly lower in chronic patients with schizophrenia than in acute schizophrenia patients. In contrast, mean (SD) total peroxide level of plasma was significantly higher in the chronic patients than in acute subjects. The mean oxidative stress index level was significantly higher in chronic schizophrenia patients than in acute age and gender matched schizophrenia patients [2.34±0.72 versus 1.41±2.12, respectively ($p<0.001$)]. Our results were consistent with the results of Dadheech *et al*. (2006), who postulated that the levels of antioxidants in chronic schizophrenia patients showed a decrease as compared to acute attributed to the antioxidant deficit due to chronic phase of schizophrenia. Our results also supports Ustundag *et al*. (2002) who pointed out that duration of schizophrenia is directly correlated with decreased plasma total antioxidants levels.

We hypothesize that oxidant stress increases in chronic phase of schizophrenia and oxidant defense systems weaken during the chronic course of the illness. Due to decreased antioxidant potential, which probably lengthens the continuous peroxides exposure and decreases the sensitivity to oxidation appears to be lower in schizophrenia patients. The patients with schizophrenia are exposed to oxidative stress and OSI may be useful to reflect the severity of the disease

CONCLUSION

Based on the presented data, free radicals and impaired antioxidants play an important role in the functioning of the brain and schizophrenia patients with positive symptoms and chronic schizophrenia patients are having more oxidative stress compared with patients having other symptoms and acute stage of illness. Until now we have not found univocal molecular basis of schizophrenia which might be due to free radicals. Further studies comprise of more number of patients are needed to explain and confirm the exact mechanisms of oxidative stress in patients with different symptoms of schizophrenia. Research concerning free radicals and antioxidative enzymes activities and supplementation with antioxidative supplements might prevent and treat schizophrenia.

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