https://doi.org/10.34883/PI.2023.14.2.004
UDC 616.895:159.944.4-071

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The Oxidative Metabolism Condition in Patients Suffering from Paranoid Schizophrenia with Continuous and Intermittent Course

Conflict of interest: nothing to declare.
Authors' contribution: M. Lyubchenko – research design development; D. Klyuev – obtaining and analysis of the data, writing the text of the manuscript; Yu. Bazyak – review of publications on the topic of the article; Zh. Bibekova – obtaining and analysis of the data, writing the text of the manuscript; K. Zarovnyy – review of publications on the topic of the article, obtaining and analysis of the data, writing the text of the manuscript.
Funding. The authors state that there was no external funding for this study.

Submitted: 11.04.2023
Accepted: 17.05.2023
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Abstract

Schizophrenia is still one of the most topical issues of modern psychiatry. According to the concept of stress diathesis, the occurrence of specific sensitivity of an individual and an impact of an environmental stressor are necessary for the condition to appear.
Purpose. Studying the condition of oxidative metabolism in the phase of acute active psychopathological disorders and in the phase of levelling of psychotic symptoms in patients suffering from paranoid schizophrenia with continuous and intermittent course.
Materials and methods. Clinical psychopathological research and biochemical blood test have been done on patients suffering from paranoid schizophrenia. Biochemical blood tests included methods of identification of lipid peroxidation products. All analyses were performed using a standard statistical package Statistica 10.0 (StatSoft Russia) and Microsoft Office Excel spreadsheets (Microsoft Corporation). All the studied groups were independent samples. At the first stage normality of distribution of obtained variables was checked using the Shapiro Wilk test. The distribution was considered normal if $p>0.05$. At the second stage, descriptive statistics tools were used. While analyzing the obtained results of the study we managed to find out signs of oxidative stress both in patients suffering from paranoid schizophrenia with continuous course at its acute stage and in those at suffering from paranoid schizophrenia with intermittent course at the time of an episode. The most evident disorders of oxidative metabolism throughout the whole study were discovered during the period of active psychopathological disorders.
Keywords: schizophrenia, stress diathesis, oxidative metabolism, lipid peroxidation, LPO

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Состояние окислительного метаболизма у пациентов, страдающих параноидной шизофренией с непрерывным и приступообразным течением

Конфликт интересов: не заявлен.
Вклад авторов: М.Ю. Любченко – разработка дизайна исследования; Д.А. Клюев – получение и анализ данных, написание текста рукописи; Ю.И. Базяк – обзор публикаций по теме статьи; Ж.Б. Бибекова – получение и анализ данных, написание текста рукописи; К.В. Заровный – обзор публикаций по теме статьи, получение и анализ данных, написание текста рукописи.

Подана: 11.04.2023
Принята: 17.05.2023
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Резюме

Шизофрения по-прежнему остается одной из наиболее актуальных проблем современной психиатрии. Согласно концепции стрессового диатеза для возникновения этого состояния необходимо появление специфической чувствительности индивида и воздействие стрессоров окружающей среды.

Цель. Изучение состояния окислительного метаболизма в фазе острых активных психопатологических расстройств и в фазе нивелирования психотических симптомов у пациентов, страдающих параноидной шизофренией с непрерывным и приступообразным течением.

Материалы и методы. Пациентам, страдающим параноидной шизофренией, было проведено клинико-психопатологическое исследование и биохимический анализ крови. Биохимические анализы крови включали методы выявления продуктов перекисного окисления липидов. Все анализы проводились с использованием стандартного статистического пакета Statistica 10.0 (StatSoft Russia) и электронных таблиц Microsoft Office Excel (корпорация Microsoft). Все исследуемые группы были независимыми выборками. На первом этапе нормальность распределения полученных переменных была проверена с помощью критерия Шапиро – Уилка. Распределение считалось нормальным, если $p>0,05$. На втором этапе были использованы инструменты описательной статистики. При анализе полученных результатов исследования нам удалось выявить признаки окислительного стресса как у пациентов, страдающих параноидной шизофренией с непрерывным течением в острой стадии, так и у пациентов, страдающих параноидной шизофренией с приступообразным течением на момент эпизода. Наиболее выраженные нарушения окислительного метаболизма на протяжении всего исследования были обнаружены в период активных психопатологических расстройств.

Ключевые слова: шизофрения, стрессовый диатез, окислительный метаболизм, перекисное окисление липидов, ПОЛ

■ INTRODUCTION

Schizophrenia is still one of the most topical issues of modern psychiatry. So far, its ethiopathogenetic mechanisms have remained understudiedd. According to the concept of stress diathesis, which dominates in the etiology of the abovementioned condition, the occurrence of specific sensitivity of an individual and an impact of an environmental stressor are necessary for the condition to appear. Thus, studying the role of biological factors has particular significance. Schizophrenic diathesis can either be caused biologically (genetic predisposition) or epigenetically by both biological and psychosocial characteristics such as alcohol consumption, trauma and social stress. The difficulty in search of biological markers of schizophrenia is related to the solution to an issue whether the given marker reflects the impact of etiological factor, just correlates with something else or is a consequence of some processes, being a link in the chain of aetiopathogenesis. A rising interest of research scientists in the pathogenesis of schizophrenia in particular and in metabolic disorders in the brain and the body in general has resulted in data collection which show a significant change in the condition of oxidative metabolism (OM) in the course of schizophrenia. Research scientists have been studying free radical reactions (FRR) and antioxidant defense (AOD) in the course of schizophrenia for a long time [1–5]. Humoral environments and mainly blood have become the most suitable substances for research. Blood is a system that responds delicately to all the changes in the human body. Moreover, there has been correlation between the changes in the properties of erythrocyte and neural membranes and the sameness of their structures. The disorder in OM in the blood of people suffering from schizophrenia has shown close correlation to that in the brain tissues. Similar correlation has been found in AOD, which shows tendency for general suppression [6–9]. The disorders in OM correlate to the duration of the disease, to the psychopathological symptom load and the intensity of personality disturbances. Therefore, the amount of data showing the impact of oxidative stress (OS) on pathophysiology of schizophrenia is constantly growing [10–12]. Potential mechanisms of aetiopathogenesis of the given disorder include genetic predisposition, some characteristics of catecholamine metabolism as well as critical environment in the CNS (glutamate, iron, fatty acids liable to acidification). The discovered link between the intensity of the disorders in OM and the activity of psychopathological disorders in the course of schizophrenia has suggested a possible pathogenetic role of these changes in OM in the disease development and has forced us to look for the means of effective correction of the abovementioned dissociations [13–16].

■ PURPOSE

Studying the condition of OM in the phase of acute active psychopathological disorders and in the phase of levelling of psychotic symptoms in patients suffering from paranoid schizophrenia with continuous and intermittent course.

■ MATERIALS AND METHODS

Clinical psychopathological research and biochemical blood test have been done on patients suffering from paranoid schizophrenia (n=110). The patients were aged between 19 and 56 with the duration of disease from 5 to 40 years. The prevailing age group were patients under 40 – 74 people (67.27%). There were 36 female patients (32.73%) aged

from 40 to 56. The average age was 36. The research suggested dividing all the patients into two groups: the first group included patients suffering from paranoid schizophrenia with continuous course (n=52). The second group was formed with patients suffering from paranoid schizophrenia with intermittent course (n=58). The control group was composed of healthy people (n=50). The method of clinical psychopathological research included studying of the mental state of the patients at time of hospital admission and over time. Studying of the mental state involved evaluation of conscious state, peculiarities of learning style and way of thinking, emotions and volition. In addition, behavioral disorders were also studied. The clinical diagnosis was determined according to the criteria of "International Classification of Diseases, 10th Edition".

Biochemical blood tests included methods of identification of lipid peroxidation products such as diene conjugates (DC), ketodienes (KD) using the method of Ushkalova V.N and Kadochnikova G.D. (1987), malondialdehyde (MDA) using the method of Goncharenko M.S. and Latipova A.M. (1985), summarized primary and secondary products, (SPP and SSP) Schiff bases (SB) using the method of Lvovskaya et al. (1991). The representants of oxidatively modified proteins of neutrophils were carbonyl derivatives (CD) of proteins and advanced oxidation protein products (AOPP).

The content of carbonyl derivatives was determined in the reaction with 2,4-dinitrophenylhydrazine using Levine R.L. et al. method [24]. The principle of the method is based on reactions of interaction of carbonyl groups of oxidated anino-acid protein residue with 2,4-dinitrophenylhydrazine resulting in dinitrophenylhydrazine formation. The amount of carbonyl derivatives was measured in nanomoles using the molar attenuation coefficient 22×10^3 $mol^{-1}\times cm\times^{-1}$. The units of measurement was $nmol/10^6$. The clynical reliability of this method had been proved, which enabled to use it to evaluate protein oxidative damage in clinical practice [23]. The content of AOPP was determined using the method of Witko-Sarsat et al. [24]. The effectiveness of antioxidant defense was evaluated according to catalase (CAT) activity using the method of Korolyuk M.A et al. (1988). The level of energy metabolism of erythrocytes was evaluated according to the adenosine deaminase (ADA) effectiveness using the method of Cronstein (1995) [17–23].

Blood sampling was conducted over time. Primary blood sampling was taken at the acute stage of the disease within the first two days of patients' hospital stay before antipsychotics (AP) had been prescribed. Secondary blood sampling was taken during the third week of patients' hospital stay in the midst of the disease on treatment with antipsychotics. The final blood sampling was taken at the time of hospital discharge on levelling of active psychopathological disorders and persisting maintaining doses of psychopharmacological agents.

All analyses were performed using a standard statistical package Statistica 10.0 (StatSoft Russia), SPSS and Microsoft Office Excel spreadsheets (Microsoft Corporation). All the studied groups were independent samples. At the first stage normality of distribution of obtained variables was checked using the Shapiro – Wilk test. The distribution was considered normal if $p>0.05$. At the second stage descriptive statistics with determination of the mean an standard deviation ($m\pm S$) – in case of normality of distribution; and with determination of the median, of the upper and lower quartiles if the distribution did not correspond to the normal law of distribution.

■ RESULTS AND CONCLUSIONS

The sinuosity of the continuous course of the disease, which is characteristic to schizophrenia in general, declared itself in periods of its acute condition and in periods of amendments of psychopathological disorders without deep remissions. During the study of patients with continuous course of the disease, the aggravation of the symptoms was represented by verbal hallucinations and commenting, dialogical and imperative pseudohallucinations. Delusions included delusions of relation, delusion of persecution and delusions of physical and mental effect. The mental status of the patients included Kandinskiy – Clerambault syndrome with the signs of ideational, sensory and motoric automatism. Our study has shown the increase of primary and secondary end products of lipid peroxidation (LPO) in patients suffering from paranoid schizophrenia with continuous course at the time of their admission to hospital. The results are shown in the tables 1 and 2 below.

Thus, the level of DK has increased by a factor of 1.9 compared to the normal range. A lot of attention is drawn to a sharp rise in the number of KD – an increase by a factor of 7.8 compared to the values in the control group. There has not been any significant

Table 1
Laboratory shift table of LPO in patients suffering from paranoid schizophrenia with continuous course at the acute stage

Values	Control group, n=50	Patients, n=52		
		Admission to hospital	At the stage of antipsychotic therapy (14–18 days of hospital treatment)	At the stage of reduction of psychotic disorders on antipsychotic therapy
DC, RU/ml	32.2±2.8	61.67±7.68*	116.65±10.04*, **	98.52±12.82*, **
KD, RU/ml	7.0±0.2	55.129±8.87*	87.62±7.33*, **	77.4±10.24*, **
MDA, micromole/ml	6.4±0.1	14.47±1.65*	12.118±0.83*	12.34±1.18*
SPP, RU	0.49±0.034	0.513±0.0577	0.705±0.07*, **	0.626±0.06
SSP, RU	0.122±0.0163	0.457±0.06*	0.553±0.057*	0.593±0.06*
SB, RU	0.069±0.0023	0.07±0.015	0.094±0.021	0.112±0.03*, **

Notes: * statistical significance (at p<0.05) compared to control group; ** statistical significance (at p<0.05) compared to admission to hospital; *** statistical significance (at p<0.05) compared to days 10 to14 of hospital treatment.

Table 2
Laboratory shift table of AOD in patients suffering from paranoid schizophrenia with continuous course at the acute stage

Values	Control group, n=50	Patients, n=52		
		Admission to hospital	At the stage of antipsychotic therapy (14–18 days of hospital treatment)	At the stage of reduction of psychotic disorders on antipsychotic therapy
CAT, nmole H_2O_2/ml erythrocyte/min	0.5±0.09	0.529±0.037	0.548±0.045	0.476±0.048
ADA, nmole ADA/ml erythrocyte/min	5.49±0.256	6.163±0.737	7.72±1.05*	11.88±2.11*, **, ***

Notes: * statistical significance (at p<0.05) compared to control group; ** statistical significance (at p<0.05) compared to admission to hospital; *** statistical significance (at p<0.05) compared to days 10 to14 of hospital treatment.

changes in the level of SB at this stage. However, we discovered a 3.7-time increase in the contents of SSP while there was no significant difference in the contents of SPP compared to that in the control group. The analysis of the values of LPO at the acute stage of psychotic disorder shows a marked activation of lipid peroxidation process which is followed by a build-up of LPO products formed at different stages of peroxide cascade. During the build-up of lipid peroxidation products in erythrocytes we could see the increase of proteolysis. In these conditions, there was no significant difference between the levels of CAT and ADA in patients from the control and study groups. The peculiarity of lipid peroxide cascade reaction is the fact that the reactions do not come to the end and generally we could see a build-up of products which are specifically attributed to the propagation of oxidation chains. The storage of lipid peroxidation products is not followed by changes in the activity of CAT and ADA in the blood of the patients. Thus, significant shifts in OM system have been registered in patients at the acute stage of paranoid schizophrenia with continuous course. The increase of LPO and OPM activation lead to the development of oxidative stress (OS) in patients' bodies.

As a result of continuous study of free radical process (FRP) at the acute stage of psychotic products it could be seen that at different stages of the study the biggest imbalance of LPO and AD system was between the 14th and the 18th days of hospital stay. At this time, the patients kept their psychotic symptoms which could even be seen on AT. The analysis of values of LPO at the acute stage of paranoid schizophrenia with continuous course has shown an increase of the primary, secondary and final products of lipid peroxidation compared to both their values in control group and to the corresponding values at the time of hospital admission (tables 1 and 2). It was found that, while in hospital, between the 14th and the 18th days patients with continuous course of the disease had shown an increase of DC values by 1.9, those of KD by 1.6, those of SPP by 1.37, compared to the same values at the time of hospital admission. There was a slight fall in the amount of MDA compared to the corresponding values at the time of hospital admission, although the amount of MDA remained twice as increased as of that of the control group. At this stage of psychotic progression, there is a tendency towards an increase of the level of SB, SSP and middle molecules. DC, which are primary products of LPO, are combinations with shifted chemical valences. A fall or an increase in the level of DC marks LPO. Their increase by a factor of 3.6 compared to the control group can be a sign of a worsening course of LPO affecting all body systems. A continuous rise in the amount of KD and an increased level of MDA, which is the most toxic product of LPO, also indicate an unfavourable tendency, that is uncontrollable multiplication of free radical reactions. Proteolysis is increasing. In the circumstances, there was no increase of the activity catalase, which is one of the key enzymes of AOD. However, there was a tendency towards an increase of the levels of ADA. By the 14th–18th day of hospital stay the levels of ADA had increased by the factor of 1.42 compared to the control group. At the stage of psychosis levelling while levelling of hallucinatory delusion with keeping the maintaining dose of AP we could see definitely increased values of DC, KD and SB by factors of 1.59, 1.4 and 1.6 correspondingly, compared to the values at the time of hospital admission. There was no significant changes in the level of MDA at the stage of reduction of acute psychotic disorders. The amount of this combination remained doubled compared to the control group. The values of SPP and SSP did not show any significant changes compared to the same values at the time of hospital admission. The study of CAT activity at this

stage of the research showed a tendency towards its insignificant downregulation. CAT is a membrane-bound enzyme and its decreased activity can be explained by membrane recombination, which appears in the presence of OS. There was an increased activity of ADA by 1.9 compared to its contents at the time of hospital admission.

The received data bear evidence to the presence of OS at all the stages of disease exacerbation. The maximum intensity of FRP corresponds to the period of active psychopositive symptoms and its therapy with adjusted dosage of AP. Clinically, the most informative values were the ones of DC, KD, MDA and SSP. Their continuous and significant increase was noticed in female patients with marked psychotic symptoms, which included a full-scale hallucinatory delusional syndrome with the signs of delusional depersonalization and severe forms of automatic behavior. High resistance to the treatment was characteristic to the abovementioned group of patients. If there is strong concentration of toxic metabolites of LPO and OPM, it is liable to cause the disease to progress.

Clinical pattern of attacks of schizophrenia with intermittent course was characterized by higher polymorphism. The structure of the attacks included affective disorders such as depression or mania. The mania was characterized by high spirits, ideational and motion activity and tendency to tangentiality. Depressive disorders were characterized by despondency, anxiety or anguish, ideational or physical retardation changing into anxious agitation. Delusional ideas of reference, delusions of persecution, delusions of affection, pseudomania, nosomania and macromania prevailed. Hallucinatory perceptual deception was represented by commenting or conversational voices; there were visual hallucination as well. The structure of the attacks included catatonic disorders in the forms of mutism and catatonic substupor. An increased amount of primary, secondary and final products of lipid peroxidation was found at the time of hospital admission of patients suffering from schizophrenia with intermittent course similar to those with continuous course of the disease. The results are shown in the tables 3 and 4 below.

Table 3
Laboratory shift table of LPO in patients suffering from paranoid schizophrenia with intermittent course of the disease

Values	Control group, n=50	Patients suffering from paranoid schizophrenia with intermittent course of the disease (n=58)		
		Admission to hospital	At the stage of antipsychotic therapy (14–18 days of hospital treatment)	At the stage of reduction of psychotic disorders on antipsychotic therapy
DC, RU/ml	32.2±2.8	70.77±4.7*	87.9±3.65*, **	69.562±3.93*, S
KD, RU/ml	7.0±0.2	59.38±4.38*	81.44±3.46*, **	73.52±4.65*, **
MDA, micromole/ml	6.4±0.1	11.155±0.72*	12.22±0.84*	11.223±1.19*
SPP, RU	0.49±0.034	0.6±0.04*	0.696±0.02*	0.57±0.028S
SSP, RU	0.122±0.0163	0.51±0.04*	0.609±0.04*	0.664±0.054*
SB, RU	0.069±0.0023	0.068±0.009	0.097±0.016	0.103±0.018*

Notes: * statistical significance (at p<0.05) compared to control group; ** statistical significance (at p<0.05) compared to admission to hospital; S – statistical significance (at p<0.05) compared to days 10 to14 of hospital treatment; SS – statistical significance (at p<0.05) compared to the values after traditional psychopharmacotherapy.

Table 4
Laboratory shift table of oxidative protein modification (OPM) in patients suffering from paranoid schizophrenia with intermittent course of the disease (as a percentage relative to the control group)

Values	Patients suffering from paranoid schizophrenia with intermittent course of the disease (n=58)		
	Admission to hospital	At the stage of antipsychotic therapy (14–18 days of hospital treatment)	At the stage of reduction of psychotic disorders on antipsychotic therapy
CD	262.2%±14.8% *	266.0%±12.3% *	233.0%±18.0% *
AOPP	181.2%±19.4*	218.5%±15.1%*	256.3%±13.1%*, **

Notes: * statistical significance (at p<0.05) compared to control group; ** statistical significance (at p<0.05) compared to admission to hospital.

There is a significant increase in the amount of DC by a factor of 2.19, that of KD by 8.48, of MDA by 1.74 compared to their level in the control group. The amount of SSP is increased by a factor of 4.18. A growth of LPO products is representative of membrane-destructive process occurring in the patients' bodies.

The record of OPM products appeared to be quite informative: the level of CD outnumbered the control values by a ratio of 2.5 to one at the time of hospital admission. Herewith, it should be noted that there was no significant positive changes in the values. On the 10^{th} – 14^{th}, day of antipsychotic therapy (APT) there were no changes whereas at the stage of reduction of psychotic disorders there was a weak tendency towards the decline of the amount of CD although it was not definite.

A dynamic pattern of AOPP contents was more definite. The level of AOPP in the blood of the patients at the time of admission to hospital was 1.8 times as increased as that of the control group but there was a tendency towards a rise of AOPP level on antipsychotic therapy. Thus, at the stage of reduction of psychotic disorders on antipsychotic therapy the level of AOPP in the blood of the patients suffering from schizophrenia increased the values of the control group by a factor of 2.56 while the difference with the level of AOPP at the time of admission to hospital was definite. The dynamics of AOPP storage can indicate a derangement of elimination of oxidized proteins from the patients' blood

Table 5
Laboratory shift table of AD in patients suffering from paranoid schizophrenia with intermittent course of the disease

Values	Control group, n=50	Patients suffering from paranoid schizophrenia with intermittent course of the disease (n=58)		
		Admission to hospital	At the stage of antipsychotic therapy (14–18 days of hospital treatment)	At the stage of reduction of psychotic disorders on antipsychotic therapy
CAT, nmole H_2O_2/ml erythrocyte/min	0.5±0.09	0.56±0.034	0.448±0.03	0.465±0.042
ADA, nmole ADA/ ml erythrocyte/min	5.49±0.256	7.28±0.7*	8.879±0.66*	12.457±2.27*, **

Notes: * statistical significance (at p<0.05) compared to control group; ** statistical significance (at p<0.05) compared to admission to hospital; S – statistical significance (at p<0.05) compared to days 10 to14 of hospital treatment; SS – statistical significance (at p<0.05) compared to the values after traditional psychopharmacotherapy.

during progressive dynamics of oxidative stress. Another mechanism could suggest increased formation of oxidized protein forms due to phagocyte activation in response to cell damage.

There was no significant change compared to normal range in the activity of CAT in this group of patients on the background of activation of LPO and OPM. The level of ADA at this stage of the study was increased by a factor of 1.3. It should be noted that there was no increase in the activity of the abovementioned enzyme in patients suffering from paranoid schizophrenia with continuous course at the acute stage of psychosis. We could not find any significant changes of CAT activity in comparison with the control group at all the stages over time. The activity of ADA At the stage of reduction of psychotic disorders remained high and even significantly increased its own level by a factor of 1.7 at the time of admission to hospital and was higher than a control value by a factor of 2.29 (table 5).

Just like at the previous stages of our research, the maximum activity of LPO and OPM corresponded to the period of active psychopathological symptoms and relief of mental status with AP. The values of LPO and OPM in all the studied products between the 14th and the 18th days of hospital stay showed a growing tendency compared to the values of alike combinations at the time of admission to hospital (table 3). The confidence level of increase was achieved for both DC and KD. Their increase was by a factor of 1.25 and 1.4 correspondingly compared to the values at the time of admission to hospital.

The phase of levelling of psychosis was characterized by the fact that the reduction of psychotic disorders on APT was not followed by full clinical improvement. The study of OM condition at this stage of APT showed a slight decrease in the level of LPO metabolites against the alike values in the phase of active psychopathological symptoms domination. However, those values remained increased against the normal range. This being said, the level of AOPP, on the contrary, showed a tendency towards a rise throughout the monitoring.

Thus, the received data show that an attack of paranoid schizophrenia with intermittent course of the disease comes amid a marked OS both at the initial stages of psychosis and at the stage of psychotic disorders reduction. Due to this fact, there is a continuous negative impact on the body along with negative toxic effects linked with metabolic disorders.

■ DISCUSSION

While analyzing the obtained results of the study we managed to find out signs of OS both in patients suffering from paranoid schizophrenia with continuous course at its acute stage and in those at suffering from paranoid schizophrenia with intermittent course at the time of an episode. The most evident disorders of OM throughout the whole study were discovered during the period of active psychopathological disorders. A growth of PLO by-products of erythrocytes in membranes leads to microviscosity increase and changes cell activity, which hampers its passage through minor capillaries. SB and other LPO products can form cross-linking with proteins and phospholipids reducing their molecular mobility. All of these lead to the development of hypoxia, which principally affect brain cells. Disintegration of respiratory chains and Krebs cycle amplifies the FRP and anaerobic glycolysis. A lot of insufficiently oxidized combinations are formed, which causes metabolic acidosis development. Primarily, all the discovered OM shifts in the patients' blood reflect the nature of OS in the brain. A relationship between the property changes in erythrocyte and neuron membranes has been found. Brain cells have hypersensitivity

to OS, which is connected with their structural features and metabolism. Hypersensitivity of brain tissue is due to oxygen saturation degree (1/5 of the total amount of oxygen in the body), predominancy of polyunsaturated fatty acids, presence of "active forms" of iron and low activity of some links of enzymic antioxidant defense. In cases of pathological state in brain tissue, there is everything necessary for intensive generation of radical products, an increase of oxidative protein and lipid destruction, which results in structural and functional damage of cell membranes. Intensification of oxidative modification of components of brain cell membranes can cause changes related to membrane ability to generate, conduct and produce nervous impulse, and malfunction of receptor, mediator and energy systems. Perhaps this is one of pathogenic links of psychotic disorders development in patient suffering from schizophrenia. The structural damage of cell membranes and changes in functional activity of receptor apparatus driven by free radical products may be most particularly linked to protein and lipid oxidative destruction.

Ethical approval

Permission for this study was obtained from the Ethics Committee of Karaganda Medical University. Signed written informed consent form was received from each participant. Confidentiality and anonymity of the respondents were maintained ensured by encrypting names with codes. The study was carried out according to the guidelines of the Declaration of Helsinki.

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