Changes in the Lipid Phase of Erythrocyte Membranes in Patients with Paranoid Schizophrenia

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Considerable changes in the lipid phase of erythrocyte membranes were found in patients with paranoid schizophrenia. During exacerbation and remission of the disease the content of phosphatidylethanolamine decreases, while the amount of lysophosphatidylcholine decreases. These changes are accompanied by an increase in erythrocyte membrane microviscosity. Structural modification of the lipid phase in erythrocyte membranes in patients with schizophrenia is associated with intensification of lipid peroxidation.

Key Words: *schizophrenia; erythrocyte; membrane; lipids*

Biological mechanisms of schizophrenia were extensively studied in the past years. There are numerous hypotheses regarding the pathogenesis of this disease. D. F. Horrobin *et al*. [11] developed the membrane conception, which suggests that lipid components of neuronal membranes undergo structural disorganization in patients with schizophrenia. This hypothesis is consistent with published data that membrane lipids act as regulators and modulators of neuronal receptors during ligand-receptor recognition and binding [7]. Recent studies revealed structural and metabolic disturbances in plasma membranes of erythrocytes [6,13, 15], platelets [14], and skin fibroblasts [12], which depend on clinical course of schizophrenia. These findings contribute to better understanding of biological mechanisms underlying the pathogenesis of schizophrenia. Here we studied the phospholipid composition of erythrocyte membranes (EM) and microviscosity of their lipid phase in patients with exacerbation and remission of paranoid schizophrenia depending on the clinical course and duration of the disease.

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MATERIALS AND METHODS

We examined 38 patients with persistent (F20.00, ICD-10) and episodic (F20.01-03, ICD-10) paranoid schizophrenia (21-49 years). The patients received no psychotropic drugs before examination. In 18 patients with schizophrenia we found acute paranoid symptoms, including pronounced affective strain, psychic automatism, pseudohallucinations, and delirious disorders. Twenty patients were examined during remission. The control group included 45 somatically and mentally healthy donors (19-48 years). Venous blood was taken after 10-12-h starvation.

EM were isolated as described elsewhere [9]. The lipid extract was obtained [10]. EM phospholipids were isolated by preparative thin-layer chromatography in a chloroform-methanol-water system (32:12.5:2) on Silufol UV254 plates [8] and identified using Sigma standards.

Microviscosity of the lipid phase in EM was estimated by pyrene eximerization at 340 nm excitation wavelength [3]. The coefficient of pyrene excimerization was calculated as the ratio between excimer (λ= 470 nm) and monomer (λ=370 nm) fluorescence maxima.

Spectral characteristics of the interaction between EM and fluorophore were recorded on an

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MPF-4 spectrofluorometer (Hitachi). The intensity of lipid peroxidation (LPO) was estimated by the content of malonic dialdehyde [1] and conjugated dienes [5] in EM.

The results were analyzed by Student's *t* test. Nonparametric tests were used for non-Gaussian distributions. The Spearman rank correlation coefficient was calculated.

RESULTS

Phospholipids are structural components of plasma membranes that regulate active and passive transmembrane transport of substances and determine cell sensitivity to ligands and activity of membrane-bound enzymes [2,4]. Analysis of the phospholipid composition of EM in patients with paranoid schizophrenia revealed a clear-cut decrease in the content of easily oxidized phosphatidylethanolamine (PEA) and accumulation of lysophosphatidylcholine (LPC) during exacerbation and remission of schizophrenia (Table 1). Since PEA playes an important role in the regulation of Ca^{2+}, Mg^{2+}-ATPase activity, the decrease in its membrane content can disturb erythrocyte ion homeostasis. Moreover, the decrease in PEA concentration is accompanied by suppression of antioxidant activity of EM lipids, which results in dysregulation of LPO [1,2]. Accumulation of LPC in EM leads to transition of the lipid bilayer into monolayer, increase in membrane permeability for Na^+ and K^+, and solubilization of enzymes [4].

In patients with exacerbation of schizophrenia the amount of phosphatidylcholine in EM decreased. Moreover, the relative content of phosphatidylinositols in EM decreased in patients with continuous progredient schizophrenia and during remission (Table 1). It should be emphasized that, phosphatidylinositols are involved in the generation of intercellular and intracellular messengers [2].

Disorganization of the phospholipid matrix in EM is probably related to accumulation of intracellular Ca^{2+} in patients with schizophrenia [14]. These changes are accompanied by the interaction of Ca^{2+} with lipid molecules and activation of Ca^{2+}-dependent phospholipase A_2, which results in accumulation of lyso-fractions and free fatty acids in erythrocytes, inhibition of aminophospholipid translocase, and changes in normal transbilayer asymmetry of membrane phospholipids [2].

Enzymatic hydrolysis of membrane phospholipids and intensification of LPO are the main mechanisms of EM modification [1]. Activation of LPO in patients with paranoid schizophrenia was manifested in excessive accumulation of MDA and conjugated dienes in EM (Table 2). A negative correlation was found between the concentration of conjugated dienes and relative content of phosphatidylinositols (r=-0.53, p<0.05) and amounts of phosphatidylcholine (r=-0.73, p<0.01) and PEA (r=-0.65, p<0.05).

Disorganization of the lipid phase in EM in patients with schizophrenia was confirmed in experi-

TABLE 1. Content of Phospholipid Fractions in Patients with Paranoid Schizophrenia (%, $\bar{X}\pm m$)

Patients	LPC	Phosphatidyl-inositols	Sphingo-myelin	Phosphatidyl-choline	Phosphatidyl-serine	PEA
Healthy donors	4.00±0.46	6.50±0.53	18.75±0.90	32.00±0.71	13.25±0.86	25.50±0.80
Stage of schizophrenia						
exacerbation	6.80±0.80**	6.40±0.97	19.60±0.92	29.80±0.56***	14.40±0.84	22.30±0.63***
remission	6.20±0.86***	5.20±0.56***	20.80±0.96	33.40±1.08^{++}	14.60±1.32	18.60±1.43***$^{++}$
Course of schizophrenia						
continuous progredient	7.00±0.66**	4.83±0.72***	20.33±0.90	33.00±1.04	14.50±0.73	20.00±0.94**
episodic	6.33±0.53***	7.67±1.03^{o}	18.67±0.60	31.00±0.71	13.33±0.65	22.67±1.21***
History of schizophrenia, years						
<5	6.24±0.67**	5.88±0.93	18.81±0.94	33.08±0.86	14.57±0.96	21.28±1.05***
5-10	6.50±0.48**	6.40±0.44	19.60±0.64	31.70±0.54	14.10±0.67	22.10±0.93***
>10	6.43±0.84**	6.43±0.58	22.07±1.84	32.67±0.74	13.63±0.84	19.07±1.31**

Note. Here and in Table 2: *p<0.001, **p<0.01, and ***p<0.05 compared to healthy donors; ^{+}p<0.001 and ^{++}p<0.05 compared to patients with exacerbation of schizophrenia; ^{o}p<0.05 compared to patients with continuous progredient schizophrenia.

TABLE 2. Lipid Peroxidation in Erythrocytes and Microviscosity of Erythrocyte Membranes in Patients with Paranoid Schizophrenia ($\bar{X}\pm m$)

Patients	MDA, nmol/mg protein	Conjugated dienes, arb. units/mg protein	Excimerization of pyrene, arb. units
Healthy donors	1.12±0.09	0.28±0.01	0.650±0.019
Stage of schizophrenia			
exacerbation	2.00±0.42***	0.81±0.14*	0.318±0.024*
remission	1.52±0.14***	0.41±0.03**+	0.385±0.017*++
Course of schizophrenia			
continuous progredient	1.73±0.36***	0.50±0.08*	0.334±0.019*
episodic	1.51±0.23***	0.64±0.12*	0.398±0.029*x
Duration of schizophrenia, years			
<5	1.80±0.34***	0.46±0.05*	0.359±0.031*
5-10	2.04±0.42***	0.51±0.09*	0.337±0.029*
>10	1.55±0.21***	0.63±0.11*	0.358±0.021*

ments with nonpolar fluorescence probe pyrene. This probe is localized in the hydrophobic layer of EM. The decrease in pyrene excimerization coefficient in schizophrenic patients (Table 2) attested to increased microviscosity of the lipid matrix in EM, which is probably related to abnormalities in lateral diffusion of protein and lipid molecules and transbilayer flip-flop [4].

Our results indicate that the lipid phase of EM undergoes considerable structural modification in patients with exacerbation and remission of paranoid schizophrenia. Similar changes in membranes of other cells (*e.g.*, reduced contents of phosphatidylserine and PEA in membranes of skin fibroblasts [12], accumulation of LPC, and decreased content of phosphoinositol in platelet membranes [14]) in patients with primary schizophrenia and relatives of probands indicate that this disorder leads to generalized disturbances and dysfunction of cell membranes.

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