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EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Serum Glutathione in Patients with Schizophrenia in Dynamics of Antipsychotic Therapy

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Serum concentrations of oxidized and reduced glutathione were measured in 73 patients with schizophrenia at admission and in dynamics of therapy with traditional and atypical antipsychotic drugs. The level of reduced glutathione in patients with schizophrenia with manifest clinical symptoms was lower than in normal subjects. Atypical neuroleptics produced virtually no effects on the glutathione system, while therapy with typical antipsychotics led to further decrease in the levels of reduced glutathione, thus aggravating the imbalance of metabolic processes typical of schizophrenia.

Key Words: *schizophrenia; reduced glutathione; antipsychotic drugs*

Activation of oxidative stress in schizophrenia is now a proven fact [2,7,14]. Some factors promote activation of free radical processes and LPO in cell membranes. Numerous studies demonstrate disorders in activities of antioxidant defense enzymes, superoxide dismutase (SOD), catalase, and glutathione-dependent enzymes [3,7,14].

Multicomponent integral regulated antioxidant system is involved in the maintenance of the optimal balance of redox processes. This system consists of enzyme and non-enzyme antioxidants maintaining the optimal proportion of redox processes. Glutathione is the most important component of nonenzymatic antioxidant defense. Low levels of reduced glutathione are detected in various brain structures of patients with schizophrenia on postmortem material, in the liquor, peripheral blood cells, and in the serum [7,12,14]. The levels of some metabolites (including glutathione) at the periphery reflect the processes unfolding in the brain; this fact suggests the peripheral blood as a model for studies of some processes in patients with mental disorders [1,12]. Some authors suggest using glutathione as a biomarker for evaluating the severity of schizophrenia course and the side effects of neuroleptic therapy [4,12,13].

Antipsychotic therapy is the basic method for the treatment of patients with schizophrenia. Drugs with different mechanisms of action have different effects on metabolism and activities of enzymes and on the pro- and antioxidant system status [9,10,13,15]. As published data on the effects of antipsychotic therapy with traditional (haloperidol) and atypical (risperidone, clozapine, *etc.*) drugs on the status of the pro- and antioxidant systems of patients with schizophrenia are miscellaneous and contradictory [10,15], it is essential to evaluate the metabolic processes in these patients before and after drug therapy with antipsychotics of different classes.

We study the effects of therapy with traditional and atypical antipsychotic drugs on serum levels of oxidized (GSSG) and reduced (GSH) glutathione in patients with schizophrenia.

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MATERIALS AND METHODS

Comprehensive clinical biological studies were carried out in 73 patients with schizophrenia. All patients gave informed consent to participation in the study. The study was carried out according to the protocol approved by Biomedical Ethics Committee of Research Institute of Mental Health and in accordance with the Helsinki Declaration for experiments including studies on humans. The criteria for including the patients into the group were the diagnosis of schizophrenia, age from 18 to 60 years, and voluntary consent of the patient to participation in the study. Patients aged over 60, with comorbid and somatic diseases impeding the objective evaluation of biochemical parameters, were not included. Psychopathological symptoms were described according to the IDC-10 manual "Rating List of Symptoms and a Glossary for Mental Disorders". Each patient was evaluated by psychosomatic scores over the course of drug therapy: PANSS (the positive and negative syndrome scale) and CGI (general clinical impression before therapy and improvement during therapy).

The patients were distributed into two groups, receiving different therapies: group 1 included 32 patients receiving typical antipsychotics (aminazine, haloperidol, and chlorprothixene) as mono- or part of combined therapy; group 2 included 41 patients receiving atypical drugs (quetiapine, azaleptin, and olanzapine).

Laboratory studies were carried out on admission to hospital before psychopharmacotherapy and after 5-6 weeks of antipsychotic therapy.

Blood specimens from 54 normal subjects served as control. The group included subjects without somatic and mental diseases (mean age 32.60±2.16 years), without chronic diseases, not registered at specialized health centers, without signs of previous acute infection by the moment of examination.

Serum GSH and GSSG were measured. Measurement of serum glutathione concentrations is based on the formation of fluorescent complex of glutathione with orthophthaleic aldehyde [8]. Optical density was measured on a Varion spectrofluorometer at λ_{em}=420 nm and λ_{ex}=350 nm. The results were expressed in μg glutathione/ml serum.

The data were processed using Statistica 6.0 software. The significance of differences between the groups was evaluated by Mann–Whitney nonparametric test. The normality of data distribution (Kolmogorov–Smirnov test) and the equality of general dispersions (Fisher's *F* test) were evaluated. The differences were considered significant at $p<0.05$.

TABLE 1. Dynamics of Serum Concentrations of GSSG and GSH in Patients with Schizophrenia Treated with Typical Antipsychotic Drugs (*M*±*SD*)

Group	GSH, μg/ml	GSSG, μg/ml
Mentally and somatically health subjects (*N*=56)	394.23±80.20	15.91±1.34
Patients before therapy (*N*=32)	298.54±41.02*	14.65±2.89
Patients after therapy (*N*=32)	261.64±20.32*	14.11±2.26

Note. Here and in Table 2: $p<0.05$ in comparison with control.

TABLE 2. Dynamics of Serum Concentrations of GSSG and GSH in Patients with Schizophrenia Treated with Atypical Antipsychotic Drugs (*M*±*SD*)

Group	GSH, μg/ml	GSSG, μg/ml
Mentally and somatically health subjects (*N*=56)	394.23±80.20	15.91±1.34
Patients before therapy (*N*=41)	303.38±35.27*	12.57±2.18*
Patients after therapy (*N*=41)	309.74±62.87	13.82±1.59

RESULTS

Disease severity on admission to hospital (PANSS scale) was 36.7±1.5 by the positive symptoms score, 41.5±2.5 by the negative symptoms score, and 51.2±3.3 by general psychopathological signs.

The level of positive symptoms was significantly lower than the mean value after a course of treatment with the typical antipsychotic drugs, while the level of negative symptoms decreased below the mean level. By the end of treatment, the PANSS score in the patients decreased by 23%. Evaluation of the treatment efficiency by CGI score by week 6 of therapy in patients treated with typical antipsychotic drugs showed marked improvement (6.25%), improvement (46.9%), or slight improvement (37.5%). No response was detected in 3 (9.35%) patients.

The dynamics of glutathione content in patients with schizophrenia before and after therapy with typical neuroleptics is presented in Table 1. The level of GSH was low in patients before therapy with typical antipsychotic drugs in comparison with control. Therapy with the typical drugs was associated with further reduction of GSH content. The content of GSSG did not differ from the control values and virtually did not change over the course of therapy.

The glutathione system is an important factor of antioxidant defense and is involved in regulation of the redox potential of the cell. In addition to the antioxidant function, reactions of the glutathione sulfhydryl group with the drug reactive group determine the formation of the drug conjugates with glutamine, thus determining the involvement of the glutathione system in drug metabolism and in xenobiotic detoxication. The numbers of glutathione SH- or SS groups are determined by the dynamic balance between the synthesis, degradation, transport, oxidation and reduction reactions and are therefore liable to change, depending on the predominance of this or that reaction, which depends on the status of the cell and the environment.

Our results, low level of serum GSH in patients with manifest symptoms, are in line with the data on unbalanced activities of glutathione-dependent antioxidant enzymes and changes in glutathione concentration [7,12,14]. The data [12] obtained in patients with the first episode or in drug naïve patients (patients without history of antipsychotic therapy) indicate that reduction of glutathione level is an etiological and pathogenetic factor, a specific feature or a biomarker of the disease. The probable causes are disorders in the functional activities of polymorphisms of the genes involved in glutathione-dependent reactions and associations of functional mutations with schizophrenia [5,6]. We have detected a two-fold drop of glucose-6-phosphate dehydrogenase activity in patients with schizophrenia in comparison with normal subjects, this drop augmenting after therapy [9]. Glucose-6-phosphate dehydrogenase-catalyzed reaction leads to formation of reduced NADP – an obligatory component of many redox processes. For example, NADPH releases H for GSSG reduction to GSH. Presumably, the decrease in the level of GSH in patients with schizophrenia is a result of lesser capacity to its reduction, for example, at the expense of a significantly lesser synthesis of NADPH in the patients.

Antipsychotic therapy can be an important factor of glutathione drop in the majority of cases. Patients with schizophrenia have to use antipsychotic drugs by long courses, often throughout life. Due to their lipophilic nature, antipsychotic drugs can incorporate in cell membranes and disorder the neuron metabolism [12]. The first-generation antipsychotic drugs can lead to ROS hyperproduction [10], disorder the activities of antioxidant enzymes, and exhibit neurotoxicity [11]. It was shown [11] that the classical and atypical antipsychotic drugs may have different effects on the cells, and the mechanisms of their activity remain unknown. Comparison of the effects of an atypical antipsychotic drug risperidone and a typical antipsychotic haloperidol on astroglia cells *in vitro* showed that risperidone increased significantly glutamate capture, activity of glutamate synthase, and GSH content, while haloperidol led to an increase of ROS production [11].

On the other hand, another team [15] has detected virtually no the differences in the intensity of changes in the antioxidant enzyme activities in the groups receiving typical and atypical antipsychotic drugs. These results indicate that, irrespective of the mechanism of action, antipsychotics, at least partially, normalize the disordered free radical metabolism.

There is no universal opinion on the effects of antipsychotic therapy on free radical processes in schizophrenia patients, and the problem therefore should be further studied [9,10,13,15].

Our results indicate a significant reduction of the level of GSH – an important component of nonenzymatic antioxidant defense – in patients with schizophrenia. Atypical neuroleptic are virtually inessential for the level of GSH, while therapy with typical antipsychotic drugs leads to its further reduction, thus augmenting the imbalance in free radical processes, intrinsic to schizophrenia. The decrease of GSH concentration in patients with schizophrenia seems to be pathogenetically based and depends on the decrease of capacity to its synthesis.

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