DOI 10.1007/s11055-021-01052-y
Neuroscience and Behavioral Physiology, Vol. 51, No. 2, February, 2021

Antioxidant Status in Paranoid Schizophrenia and Alzheimer's Disease

S. V. Sokolova,[1] M. M. Sozarukova,[2] A. N. Khannanova,[3] N. K. Grishina,[4] G. V. Portnova,[4] and E. V. Proskurnina[5]

Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 120, No. 6, Iss. 1, pp. 82–87, June, 2020. Original article submitted November 3, 2019. Accepted January 31, 2020.

Objective. To study measures of the plasma antioxidant profile in patients with paranoid schizophrenia and Alzheimer's disease (AD). **Materials and methods.** The study included 33 patients with paranoid schizophrenia and 18 patients with AD. Groups of patients with treatment-resistant schizophrenia and responding positively to treatment were identified. Measures of the antioxidant profile were determined by chemiluminometry and spectrofluorimetry. **Results and discussion.** Systemic oxidative stress due to lack of plasma low molecular weight antioxidants was not seen in AD though "thiol" protein oxidative stress was detected, providing indirect evidence of insufficiency of the glutathione system. Systemic oxidative stress was also not typical of patients with treatment-resistant paranoid schizophrenia while "thiol" oxidative stress was marked. Patients with paranoid schizophrenia and responding to therapy showed the opposite picture – systemic oxidative stress was more intense and "thiol" oxidative stress was less so. Of the neuroleptics studied, haloperidol, zuclopenthixol, risperidone, and ziprasidone had no antioxidant properties, while pericyazine, clozapine, and especially chlorpromazine had marked antioxidant properties, though they were unlikely have effects on plasma antioxidant potential. These results led to the conclusion that the glutathione component of the antioxidant system is most impaired in treatment-resistant paranoid schizophrenia and AD, while systemic antioxidant stress is minor. Oxidative impairments were less pronounced in successfully treated paranoid schizophrenia.

Keywords: antioxidant profile, paranoid schizophrenia, Alzheimer's disease.

Studies of the role of impairments to the oxidant-antioxidant balance in the pathogenesis of schizophrenia have been actively pursued throughout the world in recent decades. Most authors who have studied levels of oxidative damage makers take the view that oxidative stress occurs in schizophrenia, i.e., a state of excessive production of reactive oxygen species (ROS), and that this already occurs at the early stages [1, 2]. A quite large number of reports have also addressed antioxidant treatment. One [3] came to the conclusion that there was no effect. This is contradicted by data showing significant reductions in overall antioxidant capacity as compared with healthy controls during the first episode of schizophrenia [4, 5], in patients not receiving drug therapy [6], and in those with long-lasting ongoing illness [7], by results showing decreases in superoxide dismutase, catalase, and glutathione peroxidase activity [8] and reductions in blood [9] and brain tissue [10, 11] glutathione system activity, and by data showing reductions in the main plasma antioxidant, uric acid [12]. A number of studies have addressed the antioxidant properties of antipsychotics and their effects

[1] Medical Scientific Education Center, Lomonosov Moscow State University, Moscow, Russia; e-mail: svetlana.sokolovaf@gmail.com.
[2] Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Moscow, Russia; e-mail: s_madinam@bk.com.
[3] Gilyarovskii Psychiatric Clinic, an Affiliate of Clinical Psychiatric Hospital No. 4, Moscow Health Department, Moscow, Russia; e-mail: a.khannanova@gmail.com.
[4] Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia; e-mail: teslla@mail.ru.
[5] Bochkov Medical Genetic Science Center, Moscow, Russia; e-mail: proskurnina@gmail.com.

on antioxidant status. Of the drugs studied (clozapine, quetiapine, olanzapine, risperidone, ziprasidone, and haloperidol), olanzapine had antioxidant properties as, albeit to a lesser extent, did clozapine [13]. Prescription of antipsychotics has been suggested to have little effect on total antioxidant capacity or the blood glutathione level [12, 14].

Researchers have different views on the role of oxidative stress in Alzheimer's disease (AD), and particularly unclear is the question of whether it is a significant component of pathogenesis or a factor for progression of the disease or its sequelae [15]. The situation is complicated by the facts that the etiology of this disease remains unclear and that it occurs mainly in patients in whom systemic oxidative stress is pronounced because of age-related changes. The literature contains discussions of the role of oxidative modification of methionine in amyloid formation [16], the effects of metal catalysts of ROS reactions, i.e., copper, iron, and zinc [17], nitrosative stress [18], and impairments to mitochondrial function and energy metabolism [19]. Attention is drawn to decreased levels of glutathione in brain tissue in AD [20] and defects in the genes encoding glutathione reductase [21]. The literature contains few data on the efficacy of antioxidant therapy in AD. Among the approaches requiring consideration are the use of antioxidants improving mitochondrial function such as acetyl-L-carnitine and α-lipoic acid [22], as well as antioxidants restoring balance in the glutathione system [23, 24], though confident conclusions in relation to their efficacy are still lacking.

The aim of the present work was to study measures of the plasma antioxidant profile in patients with paranoid schizophrenia and AD and to assess the antioxidant properties of various antipsychotics.

Materials and Methods. The study cohort consisted of 33 patients with diagnoses of paranoid schizophrenia (median age 34 years, range 18–65 years) and 18 patients with AD (median age 82 years, range 64–88 years). During the study all patients were receiving treatment for disease exacerbations at the Gilyarovskii Psychiatric Clinic.

Exclusion criteria for patients were acute or chronic infections, tuberculosis, oncological disease, and decompensated diabetes mellitus.

The schizophrenia group included patients with diagnoses of paranoid schizophrenia (ICD-10 F20.0) hospitalized because of psychotic symptomatology – hallucinatory-delusional, or affective-delusional disorders. Disease duration in the study cases ranged from 1 to 20 years. All patients received antipsychotic drugs in the full amounts specified by standard care provision.

After 30 days of treatment, some patients were identified as responding to treatment (SZ^+), while others were resistant (SZ^-). Responders were patients in whom diagnostically significant symptoms of schizophrenia on the PANSS were no more than 3 points (mild) and the total assessment on the PANSS was <70 points [25]. Nonresponders were those with at least one diagnostic symptom assessed as moderate (>4 points) and a total PANSS score of >69 points despite appropriate treatment with antipsychotics. Some of the patients in this group had the continuous form of schizophrenia or the paroxysmal form of paranoid schizophrenia with protracted treatment-resistant episodes.

Biological studies were run using plasma collected into Vacutainers with lithium heparin. Samples were stored at –20°C util analysis.

The antioxidant profiles of antipsychotic drugs were measured for chlorpromazine (Aminazine, solution, 2 ml, 25 mg/ml), haloperidol (solution, 1 ml, 5 mg/ml), pericyazine (Neuleptil, 4% solution in oil, 4 g/100 ml), zuclopenthixol (Clopixol-Acuphase, solution in oil, 50 mg/ml), clozapine (Azaleptin, tablets, 25 mg), ziprasidone (Zeldox, solution, 20 mg/ml), and risperidone, (Rispolept, solution, 1 mg/ml). Azaleptin tablets were ground in a mortar and dissolved in distilled water and filtered. Chlorpromazine, haloperidol, pericyazine, zuclopenthixol, ziprasidone, and risperidone were diluted with distilled water or KH_2PO_4 buffer (100 mM, pH 7.4).

The state of the plasma antioxidant system was assessed using methods based on chemiluminometry and spectrofluorimetry to record antioxidant profiles and determine levels of antioxidant modification of serum albumin.

Recording of antioxidant profiles by kinetic chemiluminometry. Chemiluminescence was measured using a SmartLum 5773 chemoluminometer (DISoft) as described previously [26]. Luminol, 2,2'-azo-bis(2-amidinopropane) dihydrochloride (ABAP), and KH_2PO_4 were from Sigma. ABAP and luminol were mixed in the cuvette at final concentrations of 2.5 mM and 10 μM, respectively, and the required quantity of KH_2PO_4 buffer (100 mM, pH 7.4) was added and luminescence was measured at 37°C until a plateau was reached, after which 10 μl of plasma previously diluted 1:10 with buffer was added. Recording was continued for about 30 min until a new stationary level was reached. Two parameters were determined from luminograms: the area of suppression of chemiluminescence (S), which characterizes the capacity of the powerful plasma antioxidant uric acid, and the difference between the initial and final stationary chemiluminescence levels (ΔI), which characterizes the quantity of unoxidized albumin thiol groups.

Reference ranges for essentially healthy people aged 18–65 years (n = 110) were determined previously as S [195–405] and ΔI [1.2–2.2]. The state of the antioxidant deficiency corresponded to reductions in S and ΔI.

Determination of the proportion of oxidized albumin by spectrofluorimetry. After precipitation of globulins with half-saturated ammonium sulfate solution, measurements were made of plasma tryptophan fluorescence at 353 nm (λ_{ex} = 260 nm) on an RF-5301 (Shimadzu, Japan) spectrophotometer. Decreases in fluorescence were measured relative to values obtained with standard human serum albumin, i.e., the proportion of oxidized albumin (POA), which reflects the proportion of albumin modified by oxidation:

TABLE 1. Descriptive Statistics of Measures of the Antioxidant Profile in Study Groups of Patients – Median and Interquartile Ranges

Group	*S* (reference range 195–405)	Number of patients with *S* below normal	ΔI (reference range 1.2–2.2)	Number of patients with ΔI below normal	POA (reference range 0.05–0.50)
AD, $n = 18$	256 (162) N	4 (22%)	0.67 (0.38)$^-$	16 (89%)	0.34 (0.15)
SZ^+, $n = 16$	185 (105)$^-$	9 (56%)	0.78 (0.52)$^-$	10 (63%)	
SZ^-, $n = 17$	252 (107) N	4 (24%)	0.76 (0.35)$^-$	15 (88%)	
SZ (combined group), $n = 33$	218 (134)	13 (39%)	0.68 (0.41)$^-$	15 (76%)	0.37 (0.16)

$$POA = (I_0 - I)/I_0,$$

where I_0 is the calculated (theoretical) fluorescence determined from the calibration curve for the known albumin concentration and I is plasma fluorescence.

The total albumin concentration was evaluated by biochemical analysis.

The upper boundary of the reference range for POA for the group of essentially healthy people is 0.50. Values greater than this are evidence of oxidative modification of albumin.

Results and Discussion. *Antioxidant profiles of patients with schizophrenia and AD*. Antioxidant profiles of patients with schizophrenia (the SZ^+ and SZ^- groups) and AD are shown in Table 1.

Plasma antioxidant capacity (*S*) associated with uric acid was generally not reduced in AD patients – the median value was within the reference range, the number of patients with reduced capacity was small, and decrease could be assigned to age-related changes. A similar pattern was seen in treatment-resistant patients (SZ^-). As will be indicated below, the absence of oxidative stress in these patients cannot be explained by the contribution of antipsychotics. In patients with positive responses to antipsychotic treatment (SZ^+), the median value was lower than the lower boundary of the reference range and the number of patients with systemic oxidative stress was more than half the cohort (56%); three patients in this group were taking Mexidol – a drug which increases plasma antioxidant capacity. Ignoring these patients, the proportion of cases of oxidative stress in the SZ^+ group was 70%.

The parameter ΔI characterizes retention of albumin thiol groups and, indirectly, the state of the glutathione system. Both the AD group and the SZ group showed decreases in this parameter – reductions in the level of mercaptoalbumin due to depletion of the reserves of the glutathione system. The derangements were more marked among patients with more severe course of disease (SZ^-).

In the SZ and AD groups, POA was no greater than the upper limit of the reference range, which is evidence for the absence of oxidative damage to albumin.

Antioxidant properties of antipsychotics. In the analytical model used here, haloperidol, zuclopenthixol, ziprasidone, and risperidone did not have antioxidant properties. Pericyazine, clozapine (Azaleptin), and particularly chlorpromazine (Aminazine) were characterized by marked antioxidant properties. Neuroleptics with powerful antioxidant properties Azaleptin and Aminazine were used in the groups of patients with paranoid schizophrenia. All patients taking these drugs had reduced ΔI values, indicating that these drugs did not have significant protective antioxidant actions on thiol status. As for total antioxidant capacity (*S*), it seems likely that Azaleptin or Aminazine had no effect on this – the proportions of patients taking these drugs and having oxidative stress and normal values of *S* were essentially the same.

Thus, these studies yielded data characterizing the antioxidant properties of plasma: a) antioxidant capacity *S*, due to uric acid and forming the main reserve of the antioxidant defense in the plasma; b) ΔI, the level of thiol groups in albumin, the main plasma antioxidant protein, which indirectly reflects the reserves of the glutathione system; c) the proportion of oxidation-modified albumin, POA, reflecting the level of structural damage to albumin and impairments to its transport function.

The reference range for this method have previously been determined for healthy people aged 18–65 years, as it is extremely difficult to assemble a cohort of healthy older people – all the acute and chronic diseases in this population to some extent alter the plasma antioxidant profile, as does the use of various medications. Even for this reference range, the antioxidant capacity and proportion of oxidized albumin in patients with AD were in the normal range, indicating the absence of systemic oxidative stress and retention of the structure of albumin, which influences its transport function. The minor decrease in *S* in some patients may be linked with the age factor. It can be suggested that for patients with AD, prescription of water-soluble antioxidant/scavengers would be very unlikely to produce any positive pathogenetic effect.

Albumin has single thiol (SH) group, conferring its antioxidant properties. Maintenance of the ratio of unoxidized mercaptoalbumin to oxidized uses the glutathione system. Our identification of a decrease in ΔI in most patients with AD is evidence of marked "thiol" oxidative stress.

Overall, our data are consistent with results from other investigators. It has been suggested that the glutathione system suffers most in AD, as a decrease in reduce glutathione in erythrocytes has been demonstrated [27], linked with defects particularly in glutathione transferase [28, 29]. A po-

tential therapeutic approach is that of restoring the glutathione balance using antioxidants such as N-acetylcysteine and γ-glutamylcysteine ethyl ester [23].

An analogous picture was seen in patients with treatment-resistant schizophrenia (the SZ^- group), normal *S* values being evidence of the absence of systemic oxidative stress; it is unlikely that antipsychotics compensate for this on the basis of their intrinsic antioxidant properties. It is possible that this might explain the lack of positive treatment effects with agents such as vitamin C and plant flavonoids (*Gingko biloba*). The SZ^- group showed marked thiol oxidative stress, such that treatment with antioxidants restoring the glutathione balance has potential.

In schizophrenia patients of the SZ^+ group, the tendency to systemic oxidative stress was more marked, while the tendency to thiol oxidative stress was, conversely, weaker. It is apparent from our results that the more severe the schizophrenia, the closer to normal the patient's measures of antioxidant profile. These results are consistent with the concept that the activity of ribosomal genes, i.e., an adaptive resource for oxidative stress in schizophrenia, is greater than in healthy people [30]. These results require confirmation.

POA values in the schizophrenia group were within the normal range, which is evidence for retention of the spatial structure of albumin and, thus, its transport function. It can be suggested that impairment to the transport function of albumin makes a contribution to forming drug resistance in schizophrenia, though this hypothesis has not been confirmed.

Aminazine and Azaleptin have marked antioxidant properties, though comparison of the antioxidant profiles of these drugs and plasma from patients with paranoid schizophrenia in terms of chemiluminescence suggests that their use has no effect on the oxidant-antioxidant balance in plasma.

Thus, studies of the antioxidant profile using several parameters characterizing the state of antioxidant protection by plasma in AD did not identify systemic oxidative stress due to lack of low molecular weight plasma antioxidants, though "thiol" protein oxidative stress was found, evidencing deficiency of the glutathione system. Analogous results were obtained in patients with treatment-resistant paranoid schizophrenia. Patients with paranoid schizophrenia and mounting positive treatment responses had quite marked systemic oxidative stress and less pronounced "thiol" oxidative stress. These data may be useful for selecting individual most effective treatments in paranoid schizophrenia and AD.

This study was supported by the Russian Foundation for Basic Research (Grant Nos. 18-00-01511 and 17-29-06017 ofi-m).

The authors have no conflicts of interests.

REFERENCES

1. F. Ruiz-Litago, J. Seco, E. Echevarria, et al., "Adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients: a 12-months follow-up study," *Psychiatry Res.*, **200**, 218–222 (2012), https://doi.org/10.1016/j.psychres.2012.07.024.
2. J. K. Yao and M. S. Keshavan, "Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view," *Antioxid. Redox Signal*, **15**, 2011–2035 (2011), https://doi.org/10.1089/ars.2010.3603.
3. P. V. Magalhaes, O. Dean, A. C. Andreazza, et al., "Antioxidant treatments for schizophrenia," *Cochrane Database Syst. Rev.*, **2**, CD008919 (2016), https://doi.org/10.1002/14651858.cd008919.pub2.
4. T. Xie, Q. Li, X. Luo, et al., "Plasma total antioxidant status and cognitive impairments in first-episode drug-naive patients with schizophrenia," *Cogn. Neurodyn.*, **13**, 357–365 (2019), https://doi.org/10.1007/s11571-019-09530-3.
5. X. F. Li, Y. L. Zheng, M. H. Xiu, et al., "Reduced plasma total antioxidant status in first-episode drug-naive patients with schizophrenia," *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **35**, 1064–1067 (2011), https://doi.org/10.1016/j.pnpbp.2011.03.001.
6. M. Reyazuddin, S. A. Azmi, N. Islam, and A. Rizvi, "Oxidative stress and level of antioxidant enzymes in drug-naive schizophrenics," *Indian J. Psychiatry*, **56**, 344–349 (2014).
7. X. Y. Zhang, D. C. Chen, M. H. Xiu, et al., "Plasma total antioxidant status and cognitive impairments in schizophrenia," *Schizophr. Res.*, **139**, 66–72 (2012), https://doi.org/10.1016/j.schres.2012.04.009.
8. C. D. Miljevic, A. Nikolic-Kokic, D. Blagojevic, et al., "Association between neurological soft signs and antioxidant enzyme activity in schizophrenic patients," *Psychiatry Res.*, **269**, 746–752 (2018), https://doi.org/10.1016/j.psychres.2018.09.009.
9. T. K. Das, A. Javadzadeh, A. Dey, et al., "Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione," *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **91**, 94–102 (2019), https://doi.org/10.1016/j.pnpbp.2018.08.006.
10. Y. Zhang, V. S. Catts, and C. S. Weickert, "Lower antioxidant capacity in the prefrontal cortex of individuals with schizophrenia," *Aust. N. Z. J. Psychiatry*, **52**, 690–698 (2018), https://doi.org/10.1177/0004867417728805.
11. D. Matsuzawa and K. Hashimoto, "Magnetic resonance spectroscopy study of the antioxidant defense system in schizophrenia," *Antioxid. Redox Signal*, **15**, 2057–2065 (2011), https://doi.org/10.1089/ars.2010.3453.
12. J. K. Yao, R. Reddy, and D. P. van Kammen, "Reduced level of plasma antioxidant uric acid in schizophrenia," *Psychiatry Res.*, **80**, 29–39 (1998), https://doi.org/10.1016/s0165-1781(98)00051-1.
13. I. Sadowska-Bartosz, S. Galiniak, G. Bartosz, et al., "Antioxidant properties of atypical antipsychotic drugs used in the treatment of schizophrenia," *Schizophr. Res.*, **176**, 245–251 (2016), https://doi.org/10.1016/j.schres.2016.07.010.
14. M. Padurariu, A. Ciobica, I. Dobrin, and C. Stefanescu, "Evaluation of antioxidant enzymes activities and lipid peroxidation in schizophrenic patients treated with typical and atypical antipsychotics," *Neurosci. Lett.*, **479**, 317–320 (2010), https://doi.org/10.1016/j.neulet.2010.05.088.
15. M. Pohanka, "Oxidative stress in Alzheimer disease as a target for therapy," *Bratisl. Lek. Listy*, **119**, 535–543 (2018), https://doi.org/10.4149/bll_2018_097.
16. D. A. Butterfield and J. Kanski, "Methionine residue 35 is critical for the oxidative stress and neurotoxic properties of Alzheimer's amyloid beta-peptide 1-42," *Peptides*, **23**, 1299–1309 (2002), https://doi.org/10.1016/s0196-9781(02)00066-9.
17. C. Exley, E. House, A. Polwart, and M. M. Esiri, "Brain burdens of aluminum, iron, and copper and their relationships with amyloid-beta pathology in 60 human brains," *J. Alzheimers Dis.*, **31**, 725–730 (2012), https://doi.org/10.3233/jad-2012-120766.
18. A. M. Roberts, R. Jagadapillai, R. A. Vaishnav, et al., "Increased pulmonary arteriolar tone associated with lung oxidative stress and

nitric oxide in a mouse model of Alzheimer's disease," *Physiol. Rep.*, **4**, e12953 (2016), https://doi.org/10.14814/phy2.12953.

19. G. Nesi, S. Sestito, M. Digiacomo, and S. Rapposelli, "Oxidative stress, mitochondrial abnormalities and proteins Deposition: Multitarget Approaches in Alzheimer's disease," *Curr. Top. Med. Chem.*, **17**, 3062–3079 (2017), https://doi.org/10.2174/1568026617666170607114232.
20. P. K. Mandal, M. Tripathi, and S. Sugunan, "Brain oxidative stress: detection and mapping of anti-oxidant marker 'Glutathione' in different brain regions of healthy male/female, MCI and Alzheimer patients using non-invasive magnetic resonance spectroscopy," *Biochem. Biophys. Res. Commun.*, **417**, 43–48 (2012), https://doi.org/10.1016/j.bbrc.2011.11.047.
21. M. Allen, F. Zou, H. S. Chai, et al., "Glutathione S-transferase omega genes in Alzheimer and Parkinson disease risk, age-at-diagnosis and brain gene expression: an association study with mechanistic implications," *Mol. Neurodegener.*, **7**, 13 (2012), https://doi.org/10.1186/1750-1326-7-13.
22. H. H. Palacios, B. B. Yendluri, K. Parvathaneni, et al., "Mitochondrion-specific antioxidants as drug treatments for Alzheimer disease," *CNS Neurol. Disord. Drug Targets*, **10**, 149–162 (2011), https://doi.org/10.2174/187152711794480474.
23. C. B. Pocernich and D. A. Butterfield, "Elevation of glutathione as a therapeutic strategy in Alzheimer disease," *Biochim. Biophys. Acta*, **1822**, 625–630 (2012), https://doi.org/10.1016/j.bbadis.2011.10.003.
24. M. Zampagni, D. Wright, R. Cascella, et al., "Novel S-acyl glutathione derivatives prevent amyloid oxidative stress and cholinergic dysfunction in Alzheimer disease models," *Free Radic. Biol. Med.*, **52**, 1362–1371 (2012), https://doi.org/10.1016/j.freeradbiomed.2012.01.012.
25. N. C. Andreasen, W. T. Carpenter, Jr., J. M. Kane, et al., "Remission in schizophrenia: proposed criteria and rationale for consensus," *Am. J. Psychiatry*, **162**, No. 3, 441–449 (2005), https://doi.org/10.1176/appi.ajp.162.3.441.
26. A. V. Alekseev, E. V. Proskurnina, and Yu. A. Vladimirov, "Determination of antioxidants by activated chemiluminescence using 2,2'-azo-bis(2-amidinopropane)," *Vestn. Mosk. Univ. Ser. 2 Khim.*, **53**, No. 3, 187–193 (2012), https://doi.org/10.3103/s0027131412030029.
27. H. Liu, H. Wang, S. Shenvi, et al., "Glutathione metabolism during aging and in Alzheimer disease," *Ann. NY Acad. Sci.*, **1019**, 346–349 (2004), https://doi.org/10.1196/annals.1297.059.
28. G. Spalletta, S. Bernardini, L. Bellincampi, et al., "Glutathione S-transferase P1 and T1 gene polymorphisms predict longitudinal course and age at onset of Alzheimer disease," *Am. J. Geriatr. Psychiatry*, **15**, 879–887 (2007), https://doi.org/10.1097/jgp.0b013e3180547076.
29. C. Capurso, F. Panza, D. Seripa, et al., "Polymorphisms in glutathione S-transferase omega-1 gene and increased risk of sporadic Alzheimer disease," *Rejuvenation Res.*, **13**, 645–652 (2010), https://doi.org/10.1089/rej.2010.1052.
30. L. N. Porokhovnik, V. P. Pasekov, N. A. Egolina, et al., "Oxidative stress, rRNA genes, and antioxidant enzymes in the pathogenesis of schizophrenia and autism: modeling and clinical guidelines," *Zh. Obshch. Biol.*, **74**, No. 5, 340–353 (2013), https://doi.org/10.1134/s2079086414050065].