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Relation of manganese superoxide dismutase gene polymorphism with tardive dyskinesias symptoms in the Polish population

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Summary

Aim. Free radical hypothesis of TD subscribes their existence to cholinergic neurone damage in an extrapyramid system by reactive oxygen species (ROS). MnSOD contributes greatly to protection against ROS.

Methods. Schizophrenic' psychic state was evaluated with PANSS; TD increase symptoms with AIMS.

Results. Statistical gravity in allele incidence frequency and a genotype distribution was noticed between a TD and CG; also in a genotype distribution between CG and a SG. CG and TD symptoms were differentiated by allele layout, too. Relative risk for schizophrenia and TD development is dependent on a genotype in a gene for MnSOD.

Conclusions. A statistically substantial correlation was noted between schizophrenia incidence and a Val–9Val genotype in a gene for MnSOD. Schizophrenics with Val–9Val genotype in a gene for MnSOD are of nearly ten times higher risk for TD development. Risk for schizophrenia development for those having Val–9Val genotype in a gene for MnSOD is over three times higher.

gene polymorphism / manganese superoxide dismutase / schizophrenia / tardive dyskinesia

INTRODUCTION

Tardive dyskinesias (TD) are serious side effects appearing in the course of many years' neuroleptics treatment. TD occurs in 20% patients, on average, who are chronically treated by neuroleptics, though there exists a wide, from 2% to 50%, difference in occurrence dependent on the ethnic groups [1, 2]. There are several hypotheses explaining the TD pathogenesis. Many of them are concentrated on neurotransmitters systems and oxidation stress role in extra-pyramid symptoms development [3, 4]. Free radical hypothesis of tardive dyskinesia was established due to spontaneous dyskinesias (SD) occurrence observed in elder patients, not treated by neuroleptics, and not suffering from schizophrenia [5]. The hypothesis assumes that TD develops as a result of cholinergic neuron damage in the extra-pyramidal system by reactive oxygen species (ROS) [6]. They come into existence as a consequence of the intensity of catecholamine auto-oxidation process due to dopaminergic receptors' blockade by neuroleptics [7]. ROS, as mediators of a central nervous system (CNS) damage, play a key role in schizophrenia pathogenesis. It has been demonstrated many times that products' concentration of oxidation tissue damage is higher in schizophrenic patients than in healthy people [8, 9, 10]. Moreover, antioxidation enzymes in schizophrenic patients are lower than in healthy people [11, 12]. Free radical brain damage correlates to the neurodevelopmental

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paradigm of schizophrenic psychosis origin as defined by Weinberger [13].

Superoxide dismutase (SOD) plays a key role among antioxidant enzymes protecting the brain against ROS. There are three SOD isoenzymes in man: cytosole with copper and zinc in an active centre (CuZn-SOD), mitochondrial with manganese in the enzyme particle centre (MnSOD) and extra-cell SOD (ECSOD) also having copper and zinc [14, 15]. SOD is an enzyme catalyzing dismutation superoxide anion ($O_2^{\cdot-}$) to hydrogen peroxide (H_2O_2). Breathing processes in mitochondria are ROS sources in physiological conditions. Even in functionally fit mitochondria, 2% to 5% of oxygen is subject to incomplete reduction with free radical production as final products. Manganese superoxide dismutase occurring in the mitochondrial matrix is responsible for cell protection against such developed ROS [14]. Human MnSOD is not coded by mitochondrial DNA. A gene for MnSOD is found on the long arm of chromosome 6 (6q25), in the place which was presented by Moldin and Gottesman as a region candidate for schizophrenia development [16, 17].

Nowadays, only 4 functional polymorphism locations for MnSOD are known. They are Ala–9Val (GCT/GTT) in exon 2 for MTS (mitochondrial targeting sequence) – responsible for precursor protein structure, Ile–58Thr in exon 3 – responsible for protein stability and Ile–58Thr (GGA/GGG) in exon 5 and Ser–3Arg (AGC/AGA) in exon 2. Functional role of the two last polymorphisms is not known [18, 19, 20].

MnSOD, as in the case of majority of mitochondrial proteins, is relocated to mitochondria after translation as a protein containing N-final signal sequence of 24 – aminoacids length "suspended" in cytosole, and then removed during molecule transport to mitochondria. Shimoda – Matsubayashi discovered a mutation (substitution T for C) in a signal sequence changing an aminoacid in a codon 9 of this sequence from valine (GTT) to alanine (GCT). This substitution induces conformation change in MTS from structure β – sheet into α – helix [18]. As α – helix structure is necessary for effective mitochondrial transport, precursor protein with –9Ala protein signal type can be more easily transported to mitochondria than its precursor with –9Val signal type [21]. Due to this, the difference in protein sequence signal can take the form of quantity expression MnSOD in mitochondria [22].

Van Landeghen and coop. studied Ala–9Val polymorphism in MTS for MnSOD gene in various ethnic groups and they demonstrated a significant polymorphism difference between three nationality groups under study in Europe [23]. Frequency of Ala allele in Asian population is significantly statistically lower than in the studied European populations [2].

There are single studies showing, either a relation or negation, between Ala–9Val polymorphism in a signal sequence of MnSOD gene and schizophrenia [24, 25, 26].

In the context of facts presented and an undoubtful stratification effect in association researches, an interesting question seems to appear – whether Ala–9Val polymorphism in MnSOD gene in the Polish population is correlated with schizophrenia and tardive dyskinesia occurrence. Following the research, some questions have been formulated:

- Is there a genetic correlation between (Ala–9Val) polymorphism in MnSOD human gene and schizophrenia?
- Is there a statistically significant difference in (Ala–9Val) polymorphism in MnSOD human gene in tardive dyskinesia patients and persons without dyskinesias?
- Does (Ala–9Val) polymorphism in MnSOD human gene affect inception rate risk for schizophrenia and tardive dyskinesias occurrence?

MATERIAL AND METHODS

122 paranoid schizophrenia patients treated in the Adult Psychiatry Department of the Medical University of Łódź were invited to the study. Diagnosis was made according to criteria of the ICD–10 Classification of Mental and Behavioral Disorders, independently by two psychiatrists [27]. Tardive dyskinesia symptoms were found in 57 persons. Patients' clinical evaluation was performed with PANSS, while TD intensity was evaluated with AIMS [28, 29]. Considering significant fluctuations in tardive dyskinesias intensity, evaluation of extra pyramidal symptoms was made three times in weekly intervals. Arithmetic mean of the performed studies constituted the final evaluation.

Clinical and sociodemographic features of groups under study were shown in Tab.1. None of the persons taking part in the study were mentally disabled, or suffered from epilepsy, had a past history concerning psychoactive substances abuse or serious somatic illness such as diabetes, cardiac ischemia, hypertension. The control group consisted of healthy people over 45 years old with a negative family history concerning mental diseases. All, healthy and ill people, were smokers. This was because not enough non-smokers with tardive dyskinesia symptoms, who fulfilled the inclusion criteria, were found. Thus, a comparative group was selected among healthy people addicted to nicotine.

Relative risk (RR) was counted according to Svejgaard and coop. [30].

DNA was isolated from full blood with the phenol method [31]. Isolated DNA was used for amplification of MTS sequence of MnSOD human gene by applying starters: 5'CAGCAGATCGGCGGCATCAG3' and 5'CATCATCTGCGCCTTGATGT3'. The amplification product of 172bp length was etched with Bsa WI restriction enzyme and separated on 6% polyacryloamid gel. If Val–9Val was in a sample the result obtained was 87bp and 85bp. If there was heterozygote – the result was 172bp, 87bp, and 85bp and with homozygote Ala–9Val there was a picture of 172bp.

Statistical calculations were made on an IBM PC computer with the appliance of an automated statistics analysis package Statistica 5,1 PL (SN: SP818052912G5). Statistic gravity was marked for $p<0.05$. The study was given permission by Bioethics Commission of the Medical University, Łódź, decision No. RNN/17/04/KB.

RESULTS

Allele frequency and genotype distribution in the studied (Ala–9Val) gene polymorphism for MnSOD in schizophrenic patients and in the control group was demonstrated in Tab.2.

Table 3. presents genotype distribution and alleles' frequency between the control group and patients with or without tardive dyskinesia symptoms.

The control group (CG) and patients (P) under study remain in disagreement with the balance state of Hardy and Weinberg (CG $\chi^2=7.3$, df=1, p=0,001; P $\chi^2=4.64$, df=1, p=0.01).

Relative risk (RR) of schizophrenia development in persons having Val–9Val genotype in the studied polymorphism for MnSOD is over three times (RR–3.29) higher than in those lacking this genotype.

Schizophrenic patients with the Val–9Val genotype in place of functional polymorphism for

Table 1. Clinical and demographic features of schizophrenic patients with or without tardive dyskinesia and a control group

The group under study	Tardive dyskinesia symptom patients N=57	Patients without tardive dyskinesia symptoms N=65	Control group N=71
Sex (F/M)	21/36	26/39	32/39
Age (years)	56.3±10.6	54.9±9.4	50,1±7,1
Age of onset	22.9±7.3	23.4±6.7	X
Disease length (years)	29.7±11.4	30.1±10.5	X
Age of neuroleptics first dosage (years)	23.7±5.4	24.6±5.2	X
Actual neuroleptics dosage (chlorpromasine equivalent)	321.3±171.1	325.5±150.2	X
Family history of mental disease (yes/no)	22/35	20/45	0/74
Results of AIMS	5.9±3.1	X	X
Results of PANSS: P/N/G	24.5±4.9/22.2±4.7/40.9±11.9	25.0±7.5/19.0±6.2/42.1±13.1	X

Table 2. Genotypes and allele frequencies of the Ala–9Val polymorphism in schizophrenics and control group

	Allele frequency*		Genotype division**		
	- 9Val	- 9Ala	Ala/Ala	Ala/Val	Val/Val
			n, (%)	n, (%)	n, (%)
Control group (N=71)	47.89%	52.11%	25. (35.21%)	24. (33.8%)	22. (30.99%)
Schizophrenics (N=122)	73.77%	26.23%	13. (10.65%)	38. (31.15%)	71. (58.20%)

* χ^2=13.09; df=1; p<0.001; ** χ^2=20.74; df=2; p<0.001

Table 3. Genotypes and allele frequencies of the Ala–9Val polymorphism in patients with and without tardive dyskinesia

	Allele frequency [c, d]		Genotype division [a, b]		
	- 9Val	- 9Ala	Ala/Ala	Ala/Val	Val/Val
			n, (%)	n, (%)	n, (%)
Control group (N=71)	47.89%	52.11%	25. (35.21%)	24. (33.8%)	22. (30.99%)
TD patients (N=57)	89.47%	10.53%	1. (1.76%)	10. (17.54%)	46. (80.70%)
Patients without TD (N=65)	60%	40%	12. (18.46%)	28. (43.08%)	25. (38.46%)

a – control versus TD: χ^2=35.28; df=2; p<0.001; b – control versus without TD: χ^2=4.81; df=2; p=0.09; c – control versus TD: χ^2=24.51; df=1; p<0.001; d – control versus without TD: χ^2=2.00; df=1; p=0.157

manganese dismutase gene have nearly a ten times' increased risk of tardive dyskinesia occurrence (RR–9.8).

While evaluating the correlation between a genotype, alleles frequency (Ala–9Val) polymorphism and sociodemographic and clinical data of schizophrenic patients, no statistically essential correlation were observed – though close to gravity correlation between Val–9Val genotype and disease negative symptoms (p–0.075) took place.

DISCUSSION

In the 80-ties of the 20th century, it was noticed that many mental diseases were accompanied by subtle anatomical changes of encephalon structure which were connected with disordered development of central nervous system (the neurodevelopmental hypothesis) [13]. Acceptance of the research perspective of neurodevelopmental paradigm of schizophrenia turned attention to the participation of apoptosis in schizophrenia pathogenesis and to oxidation stress role as a potential source of encephalon damage [32, 33]. The aim of our research work was to study genetic association polymorphism of antioxidant enzyme with schizophrenia, as the decrease of enzyme antioxidant activity in schizophrenic patients had been demonstrated many times [11, 34, 35, 36].

The results of our study showed significant correlation between gene polymorphism for MnSOD and schizophrenia. Ala–9Ala genotype occurs more often in healthy people than in schizophrenic patients – which can be explained by its protective function. It was also proved that Val–9Val genotype is a risk factor for schizophrenia. Having this genotype increases the incidence risk by three times. Earlier studies performed on Asian population did not demonstrate any association between (Ala–9Val) polymorphism in MTS gene for MnSOD and schizophrenia [24, 25]. Akyol and coop., when working on gene polymorphism for MnSOD in the Turkish population, showed, however, a positive correlation between Ala0-Val genotype and schizophrenia [26]. They suggest, similarly to us, that Ala–9Ala genotype may protect against schizophrenia incidence. It seems that the study on Turkish pop-

ulation mentioned above, has certain limitations. The control group was selected among people of 17 to 73 years of age, and without applying positive family history as an inclusion factor. It is difficult, then, to exclude later diseases in this group as only after 45 years of age there occurs clearly less risk factor for schizophrenia incidence.

Basal nuclei are particularly threatened by oxidative damage due to intensive oxygen metabolism, high dopamine concentration and significant iron content as well as a low antioxidative enzyme activity [4]. Application of neuroleptics increases dopamine concentration in corpus striatum and indirectly increases the oxidative process [37]. It was also demonstrated that neuroleptics hinder activity of I respiratory chain complex by increasing ROS production via mitochondria. Inhibition I complex exposes the CNS to chronic oxidative stress [38]. Commonly known toxin evoking extrapyramidal symptoms 1-methyl–4-phenyl–1,2,3,6-tetrahydropiridine (MPTP) is just the mitochondrial I complex inhibitor [39]. It is believed that inhibition of I complex, not dopamine receptors blockade, causes post-medicine extrapyramidal symptoms [40]. Additionally, bivalent iron reacting with ROS (Fenton's reaction), catalyses the development of a particularly toxic hydroxyl radical which initiates lipid peroxidation [41].

It is thus an understandable fact that MnSOD, an enzyme protecting mitochondria against ROS and sweeping $O_2^{\cdot-}$, arouses significant interest from the researchers dealing with extrapyramidal symptoms in schizophrenia.

Hori and coop. demonstrated positive correlation of allele –9Val with tardive dyskinesia occurrence in schizophrenic patients, on the contrary to Zhang and coop. who did not observe essential differences in Ala–9Val polymorphism in the Chinese population of persons with tardive dyskinesia symptoms [24, 25]. The recent study, however, appears difficult to interpret as it concerned only males, but, as several studies already showed, females can constitute a risk factor for TD [42, 43]. Akyol and coop. noticed a statistically essential correlation between Ala/Val genotype and schizophrenic patients and between, mentioned above, genotype and dyskinesias presence in the Turkish population [26].

Our results demonstrate a strong correlation between functional polymorphism both in allele distribution and genotypes of MnSOD gene under evaluation. Akyol and coop. think that allele –9Val can be both a risk factor of schizophrenia and tardive dyskinesia occurrence. These observations agree with our results. In the Turkish population Ala–9Val genotype was correlated with TD symptoms. However, gravity between people with and without extrapyramidal symptoms was not demonstrated. Our studies showed a statistically significant difference between persons with and without TD symptoms in schizophrenia course.

Functional Ala–9Val polymorphism in the gene for MnSOD is responsible for an effective enzymatic protein transport to the mitochondrium where it fulfils its physiological role. MnSOD dismutases superoxide anion ($O_2^{\cdot-}$) resulting from a "leakage" of respiratory chain in the mitochondria. Due to this fact, people with Val–9Val genotype for MnSOD gene can demonstrate less expression of manganese superoxide dismutase in a mitochondrium. It results in the increased production of ROS by mitochondria. Oxidative damaged mitochondria by releasing C cytochrome and other protein factors induce apoptosis in the CNS and cause motor neuron damage [44, 45].

Apoptosis induced by $O_2^{\cdot-}$ excess in the mitochondria leads, during brain development, to discreet anatomical changes. These, during central nervous system maturing, modulate neurodevelopmental changes. The very same processes, during organism ageing, lead to cognitive functions deficiency, extrapyramidal symptoms occurrence, and finally, to progress of the illness. Paradoxically, first generation neuroleptics, inhibiting I complex mitochondria and intensifying oxidative metabolism of catecholamines, will speed these changes. The fact of tardive dyskinesia development and increase of cognitive functions deficiencies by first generation neuroleptics is commonly known by clinicians.

Summing up, it is necessary to state that in the Polish population there exists a statistically significant correlation between schizophrenia incidence and Val–9Val genotype in a gene for MnSOD. Besides, schizophrenic patients having Val–9Val genotype in a gene for MnSOD have a ten times' higher risk for tardive dyskinesia occurrence than persons not having this genotype and schizophrenia development risk in those

having the Val–9Val genotype in a gene for Mn-SOD is over three times higher than in persons not having this genotype.

REFERENCES

1. Glazer WM. Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. J Clin Psychiatry. 2000, 61: 15–20.
2. Swartz JR, Burgoyne K, Smith M. Tardive dyskinesia and ethnicity: review of the literature. Ann. Clin Psychiatry. 1997, 9: 53–9.
3. Casey DE. Tardive dyskinesia: pathophysiology and animal models. J Clin Psychiatry. 2000, 61: 5–9.
4. Tsai G, Goff DC, Chang RW. Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry. 1998, 155: 1207–13.
5. Saltz BL, Woerner MG, Kane JM. Prospective study of tardive dyskinesia incidence in the elderly. JAMA. 1991, 266: 2402–6.
6. Miller R, Chouinard G. Loss of striatal cholinergic neurons as a basis for tardive and L-Dopa-induced dyskinesias, neuroleptic-induced sensitivity psychosis and refractory schizophrenia. Biol Psychiatry. 1993. 34: 713–38.
7. Schadev PS. The current status of tardive dyskinesia. Aust NZ J Psychiatry. 2000, 34: 355–69.
8. Kuloglu M, Ustundag B, Atmaca M. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct. 2002, 20: 171–5.
9. Petronijevic ND, Micic DV, Duricic B. Substrate kinetics of erythrocyte membrane Na,K-ATPase and lipid peroxides in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2003, 27: 431–40.
10. Srivastava N, Barthwal MK, Dalal PK. Nitrite content and antioxidant enzyme levels in the blood of schizophrenia patients. Psychopharmacology. 2001, 158: 140–5.
11. Akyol O, Herken H, Uz E. The indices of endogenous oxidative and antioxidative processes in plasma from schizophrenic patients. The possible role of oxidant/antioxidant imbalance. Prog Neuropharmacol Biol Psychiatry. 2002, 26: 995–1005.
12. Yao JK, Reddy R, Mcelhinny LG. Effects of haloperidol on antioxidant defense system enzymes in schizophrenia. J Psychiatry Res. 1998, 32: 385–91.
13. Weinberger DR. From neuropathology to neurodevelopment. Lancet. 1995, 346: 552–7.
14. Halliwell B. Reactive oxygen species and the central nervous system. J Neurochem. 1992, 59: 1609–23.
15. Zelko IN, Mariani TJ, Folz RJ. Superoxide dismutase multigene family: A comparison of the Cu,ZnSOD (sod1), Mn-SOD (sod2), and EC-SOD (sod3) gene structures, evolution, and expression. Free Radic. Biol. Med. 2002, 33: 337–49.
16. Church SL, Grant JW, Meese EU. Sublocalization of the gene encoding manganese superoxide dismutase(MnSOD/SOD2) to 6q25 by fluorescence in situ hybridization and somatic cell hybrid mapping. 1992, 14: 823–5.
17. Modlin SO, Gottesman II. At issue: genes, experience, and chance in schizophrenia – positioning for the 21st century. Schizophr Bull. 1997, 23: 547–61.
18. Shimoda – matsubayashi S, Matsumine H, Kobayashi T. Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. Biochem Biophys Res Commun. 1996, 226: 561–5.
19. Borgstahl GEO, Parge HE, Hickey MJ. Human mitochondrial manganese superoxide dismutase polymorphic variant Ile58Thr reduces activity by destablising the tetrameric interface. Biocemistry. 1996, 43: 863–7.
20. Matsumine H, Saito M, Shimoda – Matsubayashi S. Localization of a gene for an autosomal recessive form of juvenile parkinsonism to chromosome 6q25.2–27. Am J Hum Genet. 1997, 60: 588–96.
21. Lemire BD, Fankhauser C, Baker A. The mitochondrial targeting function of randomly generated peptide sequences correlates with predicted helical amphiphilicity. J Biol Chem. 1989, 264: 20206–15.
22. Shimoda – matsubayashi S, Hattori T, Matsumine H. MnSOD activity and protein in a patient with chromosome 6-linked autosomal recessive parkinsonism in comparison with Parkinson's disease and control. Neurology. 1997, 49: 1257–61.
23. Van-Langeghem GF, Tabatabaie P, Kucinskas V. Ethnic variation in the mitochondrial targeting sequence polymorphism of MnSOD. Human Heredity. 1999, 49: 190–3.
24. Hori H, Ohmori O, Shinakai T. Manganese superoxide dismutase gene polymorphism and schizophrenia: relation to tardive dyskinesia. Neuropsychopharmacol. 2000, 23: 170–176.
25. Zhang ZJ, Zhang XB, Hou G. The increased activity of plasma manganese superoxide dismutase in tardive dyskinesia is unrelated to the Ala–9Val polymorphism. J Psychiatr Res. 2002, 26: 317–24.
26. Akyol O, Yanik M, Elyas H. Association between Ala–9Val polymorphism of Mn-SOD gene and schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry. 2005, 29: 123–31.
27. World Health Organization. The ICD–10 classification of mental and behavioral disorders: Clinical descriptions and diagnosis guidelines. Geneva: World Health Organization; 1992.
28. Kay SR, Opler LA. Positive and Negative Syndrome Scale (PANSS) Rating Manual. San Rafael CA: Social and Behavioral Sciences Documents; 1987.
29. Simpson GH, Angus JW. A rating scale for extrapiramidal side effect. Acta Psych Scand. 1970, 212: 11–9.
30. Svejgaard I. HLA and disease, 1982 – a survey. Immunol Rev. 1983, 70: 193.
31. Sambrook J, R`ussell DW. Molecular Clonning. A laboratory Mannual. New York: Cold Spring Harbor Laboratory Press. Cold Spring Halbor; 2001

32. Durany N, Thome J. Neurotrophic factors and the pathophysiology of schizophrenic psychoses. Eur Psychiatry. 2004, 19: 326–37.
33. Valencia A, Moran J. Reactive oxygen species induce different cell death mechanism in cultured neurons. Free Rad Biol Med. 2004, 36: 1112–25.
34. Kahl R, Kampkotter A, Watjen W. Antioxidant enzymes and apoptosis. Drug Metabol Rev. 2004, 36: 747–62.
35. Michell TM, Thome J, Martin D. Cu, Zn- and Mn – superoxide dismutase levels in brains of patients with schizophrenic psychosis. J Neural Transmission. 2004, 111: 1191–201.
36. Gałecki P, Nowakowski T. Trace elements (copper, zinc) content and superoxide dismutase activity in erythrocytes from schizophrenic patients. Acta Psychiatrica Scandinavica. 2004; S421: 14.
37. Jeste DV, Lohr JB, Manley M. Study of neuropathologic changes in the striatum following 4, 8 and 12 months of treatment with fluphenazine in rats. Psychopharmacology. 1992, 106: 154–60.
38. Karry R, Klein E, Ben Shachar D. Mitochondrial complex I subunits expression is altered in schizophrenia: a postmortem study. Biol Psychiatry. 2004, 55: 676–84.
39. Prince JA, Yassin MS, Oreland L. Neuroleptic-induced mitochondrial enzyme alterations in the rat brain. J Pharmacol Exp Ther. 1997, 280: 261–7.
40. Di monte DA, Mccormack A, Petzinger G. Relationship among nigrostriatal denervation, parkinsonism, and dyskinesias in the MPTP primate model. Mov Disord. 2000, 15: 459–66.
41. Ossowska K. Neuronal basis of neuroleptic-induced extrapyramidal side effects. Pol. J. Pharmacol. 2002, 54: 299–312.
42. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry. 1982, 37: 473–81.
43. Yassa R, Jeste DV. Gender differences in tardive dyskinesia: a critical review of the literature. Schizophrenia Bull. 1992, 18: 701–15.
44. Ben-Shachar D, Laifenfeld D. Mitochondria, synaptic plasticity, and schizophrenia. Int Rev Neurobiol. 2004, 59:273–296.
45. Joseph J, Denisova N, Strain J. Oxidative stress and age related neuronal deficits. Mol Chem Neuropath. 1996, 28: 35–40.