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Variation of genes involved in oxidative and nitrosative stresses in depression

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ABSTRACT

The dominating hypothesis among numerous hypotheses explaining the pathogenesis of depressive disorders (DD) is the one involving oxidative and nitrosative stress. In this study, we examined the association between single-nucleotide polymorphisms of the genes encoding SOD2 (superoxide dismutase 2), CAT (catalase), GPx4 (glutathione peroxidase 4), NOS1 (nitric oxide synthase 1), NOS2 (nitric oxide synthase 2), and the development of depressive disorders. Our study was carried out on the DNA isolated from peripheral blood collected from 281 depressed patients and 229 controls. Using TaqMan probes, we genotyped the following six polymorphisms: c.47T > C (p.Val16Ala) (rs4880) in *SOD2*, c.-89A > T (rs7943316) in *CAT*, c.660T > C (rs713041) in *GPx4*, c.-420-34221G > A (rs1879417) in *NOS1*, c.1823C > T (p.Ser608Leu) (rs2297518), and c.-227G > C (rs10459953) in *NOS2*. We found that the T/T genotype of the c.47T > C polymorphism was linked with an increased risk of depression. Moreover, the T/T genotype and T allele of c.660T > C increased the risk of DD occurrence, while the heterozygote and C allele decreased this risk. On the other hand, we discovered that the A/A genotype of c.-89A > T SNP was associated with a reduced risk of DD, while the A/T genotype increased this risk. We did not find any correlation between the genotypes/alleles of c.-420-34221G > A, c.1823C > T, and c.-227G > C, and the occurrence of DD. In addition, gene-gene and haplotype analyses revealed that combined genotypes and haplotypes were connected with the disease. Moreover, we found that sex influenced the impact of some SNPs on the risk of depression. Concluding, the studied polymorphisms of *SOD2*, *CAT* and *GPx4* may modulate the risk of depression. These results support the hypothesis that oxidative and nitrosative stresses are involved in the pathogenesis of depressive disorders.

1. Introduction

Depression (depressive disorder [DD]) is considered to be the most common mental disorder. Estimations show that 350 million people worldwide suffer from this disease. By the year 2020, it will have become the second most common health problem in the world, only after ischaemic heart disease [1].

The aetiology of this disease has not been examined thoroughly so far and is not completely known [2]. However, certain evidence shows that an imbalance in the generation and elimination of reactive oxygen and nitrogen species (ROS and RNS, respectively) is present during depression [3]. This imbalance leads to increased levels of biomarkers of oxidative and nitrosative process intensification, such as 8-hydroxyguanine (8-oxoG), 8-iso-prostaglandin F2α (8-izo-PGF2α), malondialdehyde (MDA), and nitric oxide (NO) [4–8]. Interestingly, a recent study has shown that increased level of MDA is associated with a reduced ability of the visual-spatial and auditory-verbal working memory and short-term declarative memory, while a high concentration of this biomarker in depressed patients' plasma may be positively correlated with the intensity of the symptoms [9]. Changes in the activity of antioxidant enzymes may be some of the reasons for the imbalance. Accordingly, it has been demonstrated that low activity of glutathione peroxidase (GPx, reduces hydrogen peroxide to

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water and reduces lipid hydroperoxides) may contribute to the development of depression [10]. Moreover, the same researchers have found that GPx activity is correlated with the severity of the disease – the lower the enzyme activity is, the more severe the symptoms are. In addition, activity of the next antioxidant enzyme, i.e. glutathione reductase (GR, reduces glutathione disulphide to the sulfhydryl form of glutathione), decreases in depressed patients as compared to healthy volunteers [9]. On the other hand, increased levels and activity of catalase (CAT, reduces hydrogen peroxide to water and oxygen) may serve as a risk factor for the occurrence of depressive episodes [11,12]. The plasma activity of another antioxidant enzyme, i.e. superoxide dismutase (SOD, catalyses the reaction of superoxide radical dismutation into oxygen or hydrogen peroxide), also increases in the course of depression, which has been proven in various experiments conducted on animal models and during clinical studies [12,13]. However, it has been proven that the over-activation of SOD may lead to the intensification of oxidative stress via H_2O_2 production [9]. A change in SOD levels has been observed in the brain tissue collected from depressed patients. An elevated level of copper/zinc (Cu/Zn) SOD has only been detected in post-mortem prefrontal cortical brain tissue, and not in the hippocampus, while the level of manganese SOD (MnSOD) has not changed in both regions of patients' brain when compared to control subjects. Different locations of these isoforms may serve as an explanation for these differences – Cu/ZnSOD is present primarily in the cytosol of glial cells, while MnSOD is found mainly in neurons and erythrocytes. So far the available results suggest that elevated levels of SOD in peripheral tissues (plasma, erythrocytes, saliva) may be reduced owing to a successful antidepressant therapy [14]. Galecki et al. (2009) found that a combined therapy with the application of fluoxetine (SSRI) and acetylsalicylic acid may lead to a decrease in the activity of Cu/ZnSOD and a reduction in MDA concentration [15]. In addition, antidepressants may also result in the normalisation of serum paraoxonase activity (reduced oxidation of apolipoprotein B containing lipoproteins) [14].

Low amounts of non-enzymatic antioxidants are considered another aspect associated with the risk of depression occurrence. So far, studies have shown that the women with DD have lower amounts of glutathione (GSH) than the women not affected by depression [16]. Moreover, a decreased concentration of GSH has been observed in the chronic mild stress animal model of the disease [17]. Similarly, the level of CoQ_{10} has been dramatically reduced in the serum of the patients suffering from DD as compared to the control group [18]. Moreover, based on an animal model, it has been possible to determine that low-zinc diet reduces the number of progenitor cells and immature nerve cells in the hippocampus of treated rats [19]. Furthermore, decreased levels of yet another group of non-enzymatic antioxidants – vitamins A, C and E – may also play an important part in the aetiology of depression; however, the results are not conclusive in this respect. On the one hand, the plasma amount of ascorbic acid (vitamin C) is reduced in the patients with DD [20]. On the other hand, it has been suggested that increased plasma levels of vitamin C can be associated with the severity of DD [21]. Results of a different study have indicated no difference in the plasma levels of vitamins A, C and E between the patients and the control group [22]. However, Maes et al. [23] found that the plasma level of vitamin E of the affected patients was lower as compared to healthy volunteers. The discrepancies in the results may be due to size differences of the studied groups, the environmental impacts and the severity of the disease. Additionally, the patients with DD are also characterised by decreased levels of other non-enzymatic antioxidants such as albumin and uric acid [9].

Another piece of evidence that supports the hypothesis of ROS and RNS involvement in the pathogenesis of the disease are changes in the level and activity of oxidative and nitrosative enzymes in the patients with DD. It has been revealed that depressed patients have increased serum levels of xanthine oxidase (XO) [3,24]. This enzyme catalyses the oxidation of hypoxanthine to xanthine and then the oxidation of xanthine to uric acid resulting in the generation of superoxide anion and hydrogen peroxide [25]. The patients with depression are characterised by elevated XO activity in the thalamus, the putamen, and the frontal and parietal cortex, the hippocampus and the caudate nuclei; XO activity has been found to be decreased in the temporal and occipital cortex [9,26]. A recent study has revealed that the main symptoms of depression – cognitive dysfunction, anhedonia and melancholia – may be associated with structural or functional neuronal changes of the putamen and the thalamus [9]. Additionally, patients with depression demonstrate increased expression of cellular NOS in the neurons of the suprachiasmatic nucleus, cornu ammonis area 1 (CA1), and subiculum regions as compared with the control group [27]. A growing body of evidence suggests that the factors involved in nitrosative stress may penetrate the blood-brain barrier exhibiting their depressive and neurotoxic activities in the brain. As a result of excessive pro-oxidative enzyme activity (such as XO, NOS), the levels of ROS and RNS are increased, which may lead to the development of neurodegenerative changes [28,29]. A large amount of ROS may induce apoptosis of neural cells by causing damage to DNA or peroxidation of the cell membrane lipid (ROS destroy the lipids of cells, mainly polyunsaturated acids [PUFAs]) [9]. This long-lasting condition may be one of the causes of death of neuronal and glial cells in the central nervous system, observed in neurodegenerative diseases [26]. Interestingly, the study suggests that the patients with DD have a reduced volume of the prefrontal cortex and the hippocampus as compared to healthy volunteers. Furthermore, a post-mortem study confirmed that the patients with DD had a reduced number and density of glial cells [14].

Moreover, the study suggested that RNS (e.g. peroxynitrite) may cause nitration of biological compounds, including amino acids (mainly tyrosine). Additionally, Maes et al. [3] have found increased levels of IgM antibodies to such modified proteins in the blood samples collected from depressed patients.

An imbalance in the production and elimination of ROS and RNS – leading to oxidative and nitrosative stress – may induce various disorders. Oxidative stress is involved in the development of cardio-vascular and neuropsychiatric disorders such as ischaemia, acute respiratory distress syndrome (ARDS), panic disorder [30], preeclampsia [31], autism [32], dementia [33], schizophrenia [34], Parkinson's disease, Alzheimer's disease [35,36], dementia [37], amyotrophic lateral sclerosis, schizophrenia and depression [14,33,34,38–41], and multiple sclerosis [42]. Moreover, a mitochondrial dysfunction can cause overproduction of ROS and – in consequence – may lead to the development of ischaemic heart disease, stroke, atherosclerosis, arterial hypertension, and hypertrophy of the myocardium [43]. On the other hand, nitrosative stress is involved in the development of Parkinson's disease [44], Alzheimer's disease [45], schizophrenia [46], depression [47], cardiomyopathy, heart failure [48], stroke, arthritis, multiple sclerosis, hypercholesterolemia, ischemia [49], and cancer [50–52].

The aforementioned studies indicate that intensification of oxidative and nitrosative stress, caused, among others, by decreased levels and activity of enzymatic antioxidants and/or excessive pro-oxidative enzyme activity, may play an important role in depression aetiology. Therefore, the aim of this study was to investigate the association between the occurrence of *SOD2*, *CAT*, *GPx4*, *NOS1* and *NOS2* polymorphisms and the risk of depression development by means of determining the frequency