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Impact of oxidative/nitrosative stress and inflammation on cognitive functions in patients with recurrent depressive disorders

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Data show that up to 38.2% of the European population have a mental disorder and that recurrent depressive disorder (rDD) is among the most commonly diagnosed disabling diseases. Over the last few years, neurocognitive impairments in rDD have become a new research front focusing on the role of cognitive decline during the course of rDD and in relation to its clinical presentation and prognosis. Both immune-inflammatory and oxidative and nitrosative stress (O&NS) processes potentially play a role in development of cognitive dysfunction in rDD. New evidence shows that chronic inflammatory and O&NS reactions occur in the brains of patients with neurodegenerative disorders and those with rDD. This narrative review presents the current state of knowledge on the possible impact of selected inflammatory and O&NS enzymes on cognitive functioning in patients with rDD. We focus on manganese superoxide dismutase (MnSOD), inducible nitric oxide synthase (iNOS), and myeloperoxidase (MPO).

Key words: inflammation • oxidative and nitrosative stress • recurrent depressive disorders • cognitive functions

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Background

Data show that up to 38.2% of the European population have a mental disorder and that recurrent depressive disorder (rDD) is among the most commonly diagnosed disabling diseases [1]. The annual prevalence of depression in the adult population is 6–12% and among people over 65 years of age it is 5–30% [2].

As a syndrome, depression often accompanies other medical and neurodegenerative diseases. This means that about 10% of all adults (about 100 million cases per year worldwide) manifest depressive symptoms. In accordance with the predictions of the World Health Organization (WHO), in the next decades of this century affective disorders (including depression) will become one of the leading causes of disability, particularly in developed countries [3].

About 50–60% of people who have recovered from the first episode of depression experience a relapse. In nearly half of the hospitalized patients, the next depressive episode occurs within the first 2 years after discharge from the hospital. It is estimated that approximately 20% of patients diagnosed with recurrent depressive disorder (rDD) experience 2 episodes of depression over a lifetime, and 60% have 3 or more (average number of phases is 3–4) [4]. Each subsequent episode is associated with a worse prognosis and often a suboptimal response to pharmacological treatment. Complete remission occurs in 50% of patients, 30% have partial remission, and 10–20% struggle with chronic disease [5].

Cognitive Function in Depression

Over the last few years, neurocognitive impairment in rDD has become a new research front, focusing on the role of cognitive decline during the course of rDD and in relation to its clinical presentation and prognosis. The efficiency of cognition significantly influences the psychosocial functioning of patients, as well as their active participation in treatment.

Cognitive impairment is increasingly regarded as a new and important target of pharmacological treatment. This approach results from a changed perception of mental illness, not only as acute symptoms such as productive or affective symptoms, but also from broader perspective.

Both genetic factors and inflammatory processes potentially play a role in development of cognitive dysfunction in rDD. In the past, it was thought that the brain is an "immunologically privileged" organ, which cannot develop inflammation. Nowadays it is known that chronic inflammatory reactions occur not only in the brains of patients suffering from neurodegenerative disorders, but also in those with rDD [6].

Neurodegenerative changes in rDD are probably caused by inflammation associated with neurotoxic actions of inflammatory cytokines, neurotoxic effects of glucocorticoids, reduced levels of polyunsaturated fatty acids, and oxidative and nitrosative stress (O&NS). All of these elements lead to the damage of fatty acids, protein, and DNA in brain cells [6].

In recent years, a special role in the etiology of rDD is attributed to 2 of the aforementioned variables: oxidative and nitrosative stress. Emotional stressors, which undoubtedly are linked to rDD, induce an inflammatory response accompanied by increased production of proinflammatory cytokines. These, in turn, stimulate the production of reactive oxygen and nitrogen species. Even stressors of low potency are associated with DNA damage as a consequence of oxidative stress, increased lipid peroxidation, and the abatement of the antioxidant system [7].

Effect of Inflammation on Cognitive Functioning

Today it is known that the central nervous system (CNS) has its own immune system, which is independent from the peripheral immune system, but constantly cooperates with it [8]. For example, engagement of immune-to-brain communication pathways by pro-inflammatory cytokines (e.g. IFN-α, IFN-γ, and IL-1) ultimately leads to microglial activation and triggers inflammatory signaling pathways [9]. Upon activation, microglia up-regulate expression of detrimental factors of reactive oxygen species such as nitric oxide via inducible nitric oxide synthase (iNOS) and induce oxidative stress, contributing to neuropsychiatric pathogenesis [10]. Many studies have indicated that systemic inflammation enhances immune response in the CNS, and indirectly leads to cognitive deficits [11].

Oxidative stress

Oxidative stress is characterized by increased activity of free radicals (*reactive oxygen species*, ROS). It develops as a result of imbalances between production and degradation of toxic derivatives of oxygen (increasing levels of free radicals and their reaction products exceed the possibilities of elimination). Severe imbalance between the oxidant and antioxidant systems can lead to irreversible changes in the body and contribute to tissue damage in a variety of disorders [12]. Overproduction of oxygen free radicals plays an important role in the mechanism of chronic inflammation. If ROS accumulate, they activate protection systems [13].

The brain is particularly susceptible to oxidative damage because the brain uses large amount of oxygen and is built of cells with high levels of lipids, including unsaturated fatty acids that easily react with the free radicals. Moreover, certain areas of the human brain contain significant amounts of metal

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ions, especially Fe3+, Cu2+, and Zn2+, which promotes the formation of ROS. Moreover, lower concentrations of antioxidants are observed in CNS tissues as compared to other organs [14]. The cells of the hippocampal CA1 region (Sommer sector) and CA4 (Bratz sector), the cells in the dorsal-lateral striatum, and neurons of III and V layers of the cortex are regarded as the most sensitive to damage [6].

Excessive production of ROS, insufficient activity of antioxidant defense mechanisms, and central inflammatory reactions are considered to play a role in the pathogenesis of a growing number of diseases, including many CNS disorders. At the top of the list are neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and stroke [15,16]. In many of these diseases (e.g. Alzheimer's disease) O&NS is accompanied by mild cognitive impairment [17].

In rDD we found that a decrease in visual-spatial and auditory-verbal working memory span and declarative memory is associated with elevated levels of malondialdehyde (MDA – a product of lipid peroxidation, which is regarded as an indicator of the effectiveness of the body's antioxidant defense system and also of the damage caused by reactive oxygen species) [18], increased levels of nitric oxide (NO) [19], and reduced level of total antioxidant status (TAS) [20]. Patients with major depression have reduced plasma oxygen radical absorbance capacity as compared to healthy individuals [21].

Inflammatory and O&NS Enzymes

Several papers have stressed the importance of inflammatory and O&NS enzymes in the etiology of depressive disorders. These include manganese superoxide dismutase (MnSOD), myeloperoxidase (MPO), and inducible nitric oxide synthase (iNOS) [22,23]. These compounds participate in the inflammatory response and are also involved in the production of free radicals and consequent O&NS damage of proteins, fatty acids, and cell DNA [24]. These processes may cause brain damage by impairment of neurogenesis and intensification of neurodegenerative processes [25]. Interestingly, expression of antioxidative enzymes like heme oxygenase-1 (HO-1) can reverse oxidative stress and may characterize antidepressant and neuroprotective mechanisms [26,27].

Increased expression of genes encoding the above-mentioned inflammatory and O&NS enzymes were also observed in many other diseases whose symptoms include cognitive impairment, for example COX-2 genetic variations in depression [27], COX-2 mRNA levels in patients with asthma [28] and Alzheimer's disease [29], MPO expression at the protein level in patients with AD [30], multiple sclerosis [31], asthma [32], and finally, increased expression of iNOS in asthma patients [33].

In the following sections we review the possible impact of manganese superoxide dismutase (MnSOD), inducible nitric oxide synthase (iNOS), and myeloperoxidase (MPO) on cognitive functioning in rDD patients.

Manganese Superoxide Dismutase

MnSOD (SOD-2) forms the first line of defense against damage caused by excessive mitochondrial production of superoxide anion radical [24]. Recent studies indicate that MnSOD protects cells from apoptosis in the hippocampal CA1 region [34]. Moreover, MnSOD prevents release of free radicals in the hippocampal CA3 region during excessive glutamatergic activity [35]. Mice with reduced levels of MnSOD are more vulnerable to oxidative stress and have increased mortality [36].

Increased levels of SOD-2 in rDD patients in comparison to healthy subjects have been observed in many studies [14]. However, Herken et al. [37] and Selek et al. [38] obtained opposite results. The latter study included patients with depressive phase of bipolar disorder (n=30) and found that baseline levels of SOD-2 were decreased (when compared to healthy controls) and increased after 30 days of pharmacological treatment. Gałecki et al. [39] demonstrated that the polymorphisms of the MnSOD gene (Ile-58Thr and Ala-9Val) in rDD patients are associated with the development and course of disease. Pietras et al. [40] reported analogous results obtained in a different population. In patients with chronic obstructive pulmonary disease (COPD), Val/Val genotype at position 9 of the MnSOD signal peptide is associated with severity of depression, anxiety as a trait, and anxiety as a state in comparison to individuals with genotype Val/Ala and Ala/Ala. Decreased levels of MnSOD in the group of patients with depression compared to the control group may therefore indicate a dysregulation of defense systems against the negative effects of O&NS.

Reduced expression of MnSOD in neurons in the cerebral cortex, cerebellum, and basal ganglia is connected with neurodegeneration [41]. Michel et al. [42] showed that reduced volume of the prefrontal cortex and hippocampus in patients with major depressive disorder is associated with changes in the concentration of MnSOD. No reports are available that combined mRNA expression and/or the protein level of MnSOD with the efficiency of cognitive function. The influence of aberrant MnSOD expression on aging has been described in numerous studies based on animal models [43] and research in human subjects [44]. Furthermore, the authors of the latter work [44] emphasize the positive correlation between single nucleotide polymorphism rs4880 (CC/CT) of MnSOD gene, and results of MMSE and length of life among 1650 respondents aged over 90 years. Dumont et al. [45], in a study based on an animal model, showed that the expression of MnSOD is an

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important factor in the reduction of oxidative stress, effectiveness of visual-spatial memory, and prevention of Alzheimer's disease. Deficiency of antioxidant defenses by MnSOD leads to increased deposition of amyloid plaques [46], higher phosphorylation of tau protein [47], and accelerates the onset of behavioral changes [48] in an animal model of AD. However, according to Hu et al. [43], there is no association between increased expression of MnSOD, memory efficiency, and long-term potentiation (LTP) (research based on animal models).

Inducible Nitric Oxide Synthase (iNOS)

Research over the past few years underlines the importance of nitric oxide in the pathophysiology of depression [49,50]. Nitric oxide plays a crucial role, not only in multiple biological processes, but also in the regulation of cognitive and emotional functions, suggesting that nitric oxide is important in the etiology of anxiety disorders and depression (primarily through participation in neuromodulation, neurotransmission, and synaptic plasticity) [51]. Nitric oxide, one of the free radicals, is involved in the regulation of oxidative stress [24]. Under physiological conditions, nitric oxide has neuroprotective properties, but when produced in excess or when the cells are under oxidative stress, nitric oxide becomes harmful. During oxidative processes and reduction of NO, reactive nitrogen species (RNS) are formed, which are toxic substances that may cause cell damage. Both NO and RNS play a role in the pathogenesis and development of a number of neurodegenerative diseases [52].

iNOS is 1 of the 3 isoforms (together with neuronal – nNOS and endothelial – eNOS nitric oxide synthase), responsible for the synthesis of nitric oxide [53]. iNOS plays a crucial role in inflammatory processes, and inhibition of iNOS may result in an antidepressant effect. Increased iNOS expression may be observed in astrocytes, microglia cells, endothelial cells, and immature neurons in various regions of the brain [54]. Madrigal et al. [55] described the increased expression of iNOS in the hippocampus and cerebral cortex as a result of experienced stress. Gałecki et al. [56] observed increased mRNA expression of iNOS gene in patients with rDD episodes. Selek et al. [38] demonstrated increased levels of NO in patients with depressive phase of bipolar disorder compared to healthy subjects. Kim et al. [57] found significantly higher levels of NO in the blood/plasma of 39 patients with depressive disorder who had attempted to commit suicide, as compared with depressed patients without a history of suicide attempts and to healthy subjects. In depression, particularly chronic depression, Maes et al. [58,59] found increased IgM-mediated autoimmune responses against many NO-adducts, showing that (chronic) depression is associated with chronically elevated levels of nitric oxide, which have damaged proteins causing autoimmune responses. In cellular models, Su et al. found iNOS regulation is associated with depression induced by cytokines [9] and the antidepressant effects of omega-3 fatty acids and antidepressant drugs [26].

In 1997, McCann [60] launched the hypothesis that nitric oxide plays a key role in the ageing process. According to this theory, repeated infections in the CNS and other organs can lead to increased expression of iNOS in the brain, leading to the degeneration of neurons and glia, and consequently to cognitive deficits. iNOS is activated several hours after the activation of the pathogen and produces nanomolar amounts of NO over several hours or even days [60].

Increased expression of iNOS was found in the hippocampal CA1 region in patients with depressive disorders [61] and in the nuclei of the cerebellum in animal models of depression [62]. Elevated levels of iNOS are also observed in Parkinson's disease [63] and in Alzheimer's disease [64]. According to Eckel et al. [65], decreased iNOS activity is associated with improved immediate memory, and Gökçek-Sarac et al. [66] found that the increased activity of iNOS in the hippocampus affects the ability to learn new information.

Old age is probably associated with the overproduction of iNOS in the hippocampus and cerebral cortex [67]. Animal models reveal that with increasing age, iNOS expression is elevated in the hippocampus and cerebral cortex, phenomena which are accompanied by loss of memory efficiency and capacity. In addition, activation of immune cells involved in the production of iNOS is associated with decreased memory performance [Xu 2011]. Overproduction of iNOS in response to hypoxia also leads to memory impairment, especially consolidation of memory traces, via disruption of the cholinergic system [68].

Myeloperoxidase (MPO)

Myeloperoxidase is a peroxidase enzyme expressed in neutrophils and released during immune-inflammatory responses [69]. It is a surrogate marker of inflammation and pro-oxidative processes in patients with depression [69].

Gałecki et al. [56] described increased mRNA expression of the MPO gene in patients with rDD (n=181) compared to healthy controls. Moreover, Gałecki et al. [69], by analyzing single nucleotide polymorphism (SNP) G-463A of the MPO gene, demonstrated differences in the distribution of genotypes and allele frequencies between patients with rDD and healthy subjects. Homozygous G-463G and -463G alleles were found significantly more often in rDD. This confirms the relationship between the presence of genotype G-463G and -463G allele and the risk of depression.

Several years ago, a significant association between serum MPO concentrations and the risk of coronary heart disease

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(CHD) was detected [70]. In people with a total or partial MPO deficiency, the risk of CHD is significantly lower. Also, depressive disorders are considered to be one of the risk factors for CHD. Both diseases have inflammatory and O&NS pathways, as well as cognitive impairment [71].

MPO enzyme activity and high expression is observed in the healthy brain. Increased MPO expression is associated with neurodegeneration and higher risk of developing Alzheimer's disease. The gene encoding myeloperoxidase may be associated with the formation of β-amyloid plaques [72]. Mann et al. [72] noted the importance of a functional polymorphism (G/A) of gene encoding MPO for cognitive functions in patients with multiple sclerosis, but the results showed no statistically important relationship between analyzed variables. In turn, Pope et al. [73] reported a link between G-463A polymorphism in the promoter region of the gene MPO and cognitive functions. For patients with the AA genotype, the risk of cognitive deficits was 1.58 times greater than that of patients with genotype AG, and 1.96 times higher than for those with the GG genotype. According to the authors, AA genotype is associated with a decrease in the production of MPO. MPO is involved in the induction of neuronal death and inhibition of neurogenesis [74].

Conclusions

In most of these of the cited works, expression of enzymes was obtained from peripheral blood, but these peripheral changes can affect the functioning of the brain structures [56]. It can be concluded that, even if there is no expression of the gene described in the brains of patients with depressive disorders, it is likely that the process of brain diseases results from peripheral pathology [56,75]. Further research in this is necessary.

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