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Effects of Propofol on Oxidative Stress Parameters in Selected Parts of the Brain in a Rat Model of Parkinson Disease

Wpływ propofolu na parametry stresu oksydacyjnego w wybranych częściach mózgu w modelu doświadczalnym u szczurów z chorobą Parkinsona

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: Propofol is an intravenous sedative-hypnotic agent that is commonly used to induce and maintain general anaesthesia. This drug has antioxidant properties, which are partly caused by a phenolic structure similar to α-tocopherol. The present study aimed to evaluate the effect of propofol on the level of oxidative stress biomarkers in the frontal cortex, striatum, thalamus, hippocampus and cerebellum in rats with experimental Parkinson's disease (PD).

Material/Methods: The experiment was performed on 24 male Wistar rats assigned to the following groups: 1 – control; 2 – PD; 3 – PD with propofol. The dopaminergic systems were damaged with 6-hydroxydopamine (6-OHDA) administered to each lateral ventricle (2x15 μg/5 μl). 60 mg/kg of propofol was later given to the 8-week-old rats intraperitoneally. The activities of superoxide dismutase (SOD) and its enzymes Cu/ZnSOD and MnSOD, together with the malondialdehyde (MDA) concentration, total oxidative status (TOS) and total antioxidant capacity (TAC), were measured.

Results: In the 2nd group, a significant increase in MDA concentration in the striatum, hippocampus and thalamus, and an increase of TOS in the striatum, thalamus and cerebellum were noted, along with a TAC decrease in the cortex, striatum and thalamus. Propofol caused a significant decrease in MDA levels in the cortex, striatum, hippocampus and thalamus, and a decrease in TOS levels in the cortex, striatum and cerebellum, with increased TAC in all evaluated structures.

Conclusions: A shortage of natural antioxidants is observed in PD, along with an increase in pro-oxidants in many brain areas. Propofol inhibits oxidative stress in the brain, which shows its neuroprotective properties against oxidative damage.

Keywords: **Parkinson disease • oxidative stress • antioxidant enzymes • malondialdehyde • propofol, rats**

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Abbreviations: **Cu/ZnSOD** – cytoplasmic Cu/Zn-Superoxide dismutase, **MDA –**malondialdehyde, **MnSOD –** mitochondrial Mn-superoxide dismutase, **6-OHDA –** 6-hydroxydopamine, **PD** – Parkinson's disease, **ROS –** reactive oxygen species, **SOD –** superoxide dismutase, **TAC** – total antioxidant capacity**, TOS –** total oxidative status.

Introduction

Propofol (2,6-diisopropylphenol) is a short-acting, intravenous anaesthetic agent that is commonly used in anaesthesiology to induce and maintain anaesthesia. Propofol has gained wide recognition not only due to its unquestionable anaesthetic properties, but also to the number of non-anaesthetic effects. This drug exhibits strong antioxidant, immunomodulatory, anxiolytic and neuroprotective properties [16,31]. Neuroprotective effects of propofol are attributed to its ability to directly scavenge free radicals and strengthen the antioxidant defence of cells by increasing the activity of antioxidant enzymes [9,10,27]. This drug can be potentially useful in the treatment of brain diseases related to oxidative stress [10]. Previous research has also shown that propofol can potentiate the anti-Parkinson effects of standard treatment, but these mechanisms are not fully understood [17]. All these beneficial properties of propofol may expand its clinical use in the future. Antioxidant properties of propofol are partly caused by the presence of a phenolic hydroxyl group in its chemical structure, which is capable of directly scavenging free radicals. On the other hand, it seems that this is not the only way this drug works [9]. It has been shown that the activity of propofol antioxidant mechanisms are different in each cell and that different mechanisms may be involved in regulation of the oxidant-antioxidant system. The initial state of oxidative-antioxidative potential of the cell also seems to be not without significance [23,24,29]. The antioxidant properties of propofol have been evaluated in several models of oxidative stress [20,24,29] and clinical studies [4], but there are no studies analysing the effect of propofol on the level of oxidative stress in different brain structures in Parkinson's disease (PD).

This study aimed to assess the effect of propofol on selected parameters of the oxidant-antioxidant system in the cerebral cortex, striatum, thalamus, hippocampus and cerebellum in an animal model of PD induced by 6-hydroxydopamine (6-OHD) administration. It has also been evaluated whether propofol can inhibit oxidative stress in these structures, and thus protect the brain tissues from oxidative damage.

Materials and methods

Animals

All experimental procedures were approved and controlled by the Animal Experiments Local Ethics Committee of the Medical University of Silesia in Katowice (permit no. 33/2013). Once approved, the experiment was conducted in accordance with the NIH Guidelines for Animal Care as described in the *Principles of Laboratory Animals Care*.

In this study, 24 male Wistar rats were used. The procedures of the experiment were performed on newborn Wistar rats and animals that had just reached maturity. The animals were housed in cages in a well-ventilated room, throughout the study, with a constant temperature (22 ± 1°C) with a 12hour light and dark cycle. Rats had free access to filtered water and standard laboratory chow.

Experimental model of Parkinson's disease

Newborn Wistar rats were separated into two groups and treated as follows:

Group I: control rats. Desmethylimipramine (20 mg/kg body weight in a 1.0 ml/kg body weight volume) was intraperitoneally (IP) administered to 3-day-old animals. After one hour, 10 µl of 0.1% ascorbic acid solution intracerebroventricular (ICV) administration was performed.

Group II: rats with Parkinson's disease. Desmethylimipramine was administered to 3-day-old animals (20 mg/kg body weight in a 1.0 ml/kg body weight volume by IP). After one hour, 6-hydroxydopamine (6-OHDA) in a dose of 15 µg in 5 µl of 0.1% ascorbic acid solution was administered into each lateral ventricle of the brain.

6-OHDA used in the experiment is a neurotoxin which, when applied to the lateral ventricles of the brain, causes a persistent, lifelong destruction of the dopaminergic nigrostriatal pathway and profound deficits of dopamine in the striatum. Rats lesioned shortly after birth with 6-OHDA are posed as a near-ideal model of advanced stage Parkinson's disease, because the neuroanatomical and neurochemical indices in this model reflect the dopaminergic destructions in patients with severe PD, as was described by Kostrzewa et al. [14,15].

Experimental design

Animals were housed with their mothers until their 28th day of age, and then were divided by gender and placed in separate cages. Further studies were performed using 24 male Wistar rats divided into groups of 8 as follows:

- Group 1: control rats treated with 1.0 ml/kg body weight IP 0.9% NaCl solution.
- Group 2: rats with PD treated with 1.0 ml/kg body weight 0.9% NaCl solution IP.
- Group 3: rats with PD treated with 60 mg/kg body weight propofol IP.
- Administration of propofol and 0.9% NaCl was performed once, 60 minutes prior to decapitation.

Tissue storage and preparation

Animals were sacrificed by decapitation at 8 weeks of age, then after the opening of the skull, their brains were immediately removed and the following structures were dissected: frontal cortex, striatum, thalamus, hippocampus and cerebellum. Tissues were placed on solidified CO_2, weighed and stored until further analysis at a temperature of -80ºC. Tissue homogenization was performed using an UP50H ultrasonic processor (Hielscher), cooling the samples with ice. The homogenates were centrifuged at 3000 rpm for 10 minutes and the resulting supernatants were used to determine the oxidation-antioxidation parameters.

Biochemical analysis

The concentration of malondialdehyde (MDA) was determined in brain homogenates using the reaction with thiobarbituric acid, according to the method described by Ohkawa [18]. An LS45 Perkin Elmer spectrofluorimeter at a wavelength of 515 nm (absorbance) and 522 nm (emission) was used for reading. This method was modified by the addition of sodium sulfate, and butylated hydroxytoluene, which further increased the specificity of the method. MDA concentration was expressed in µmol/g protein. The method of Oyanagui was used to measure the activity of superoxide dismutase (SOD) and its isoenzymes in brain homogenates [19]. In this method, xanthine oxidase produces superoxide anions which react with hydroxylamine to form nitric ions. These ions react with naphthalene diamine and sulfanilic acid, generating a coloured product. The concentration of this product is proportional to the amount of produced superoxide anions and negatively proportional to the activity of SOD. Absorbance was measured using a Shimadzu UV-1700 spectrophotometer at a wavelength of 550 nm. The enzymatic activity of SOD was expressed in nitric units. The activity of SOD is equal to 1 nitric unit (NU) when it inhibits nitric ion production by 50%. Activities of SOD were normalized to milligrams of protein in homogenates (NU/g protein). The total oxidative status (TOS) was measured by the method described by Erel [5]. This method is based on the oxidation of Fe^{2+} ions to form Fe^{3+} by oxidizing materials, contained in the sample, in an acidic environment and consists of measuring the colour intensity of Fe^{3+} ion complexes with xylenol orange. The measurements were performed using an EM280 biochemical analyser. The concentration of TOS was expressed in µmol/g protein. Total antioxidant capacity (TAC) was measured by the method described by Erel [6]. This method is based on the decolourization of oxidized ABTS under the effect of antioxidants contained in the examined material. TAC was expressed in µmol/g protein.

Statistical analysis

All statistical analyses were done with the STATISTICA 10 software. The normality of the results distribution was verified using the Kolmogorov–Smirnov test. The analysis of variance (ANOVA univariate and bivariate) and Newman–Keuls post hoc test were applied. The Kruskal–Wallis test was used for nonparametric data. The significance criterion was $p < 0.05$.

Results

We observed a decrease in TAC in the Parkinson's disease group (group 2) in the cortex, striatum and thalamus) compared with the control group (group 1). In the Parkinson's disease group with administered propofol (group 3) we observed a statistically significant increase in TAC in all studied brain parts compared to the group with Parkinson's disease (group 2) (Figure 1).

We observed a statistically significant increase in TOS in the striatum, thalamus and cerebellum of the Parkinson's disease group (group 2) compared with the control group (group 1). In the Parkinson's disease group with administered propofol (group 3) we observed lower levels of TOS compared to group 2 and a statistically significant increase in TAC in the cortex, striatum and cerebellum (Figure 2).

Considering SOD activity we observed a statistically significant decrease in the Parkinson's disease group with propofol (group 3) in the cortex, striatum and hippocampus compared to the group without propofol (group 2). MnSOD activity decreased in the cortex and increased in the thalamus and cerebellum of group 3 compared with the group 2. Cu/ZnSOD decreased in the cortex and hippocampus of the 2nd group compared

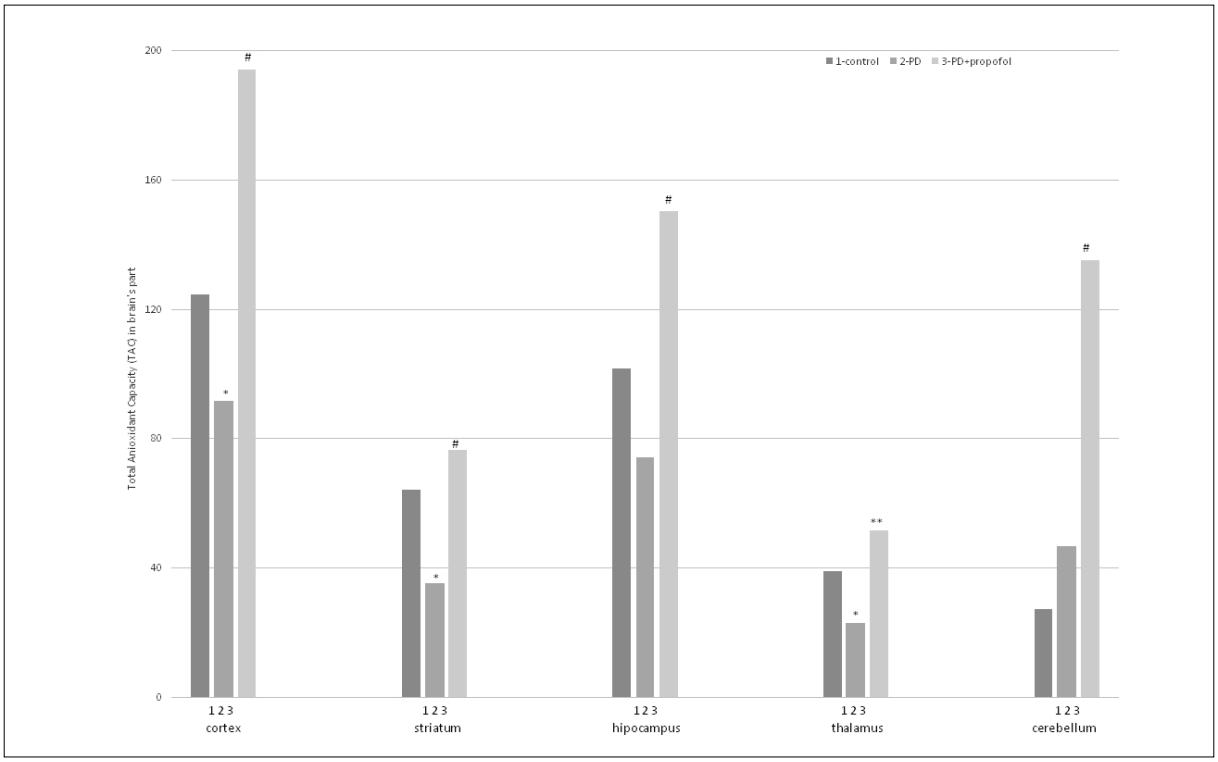

Fig. 1. Total Antioxidant Capacity (TAC) in brain's part of the control group, Parkinson's disease group and Parkinson's disease group after administration of propofol. * 1*vs*2 - p<0.05; ** 2 *vs*3 - p<0.05; #2*vs*3 - p<0.001

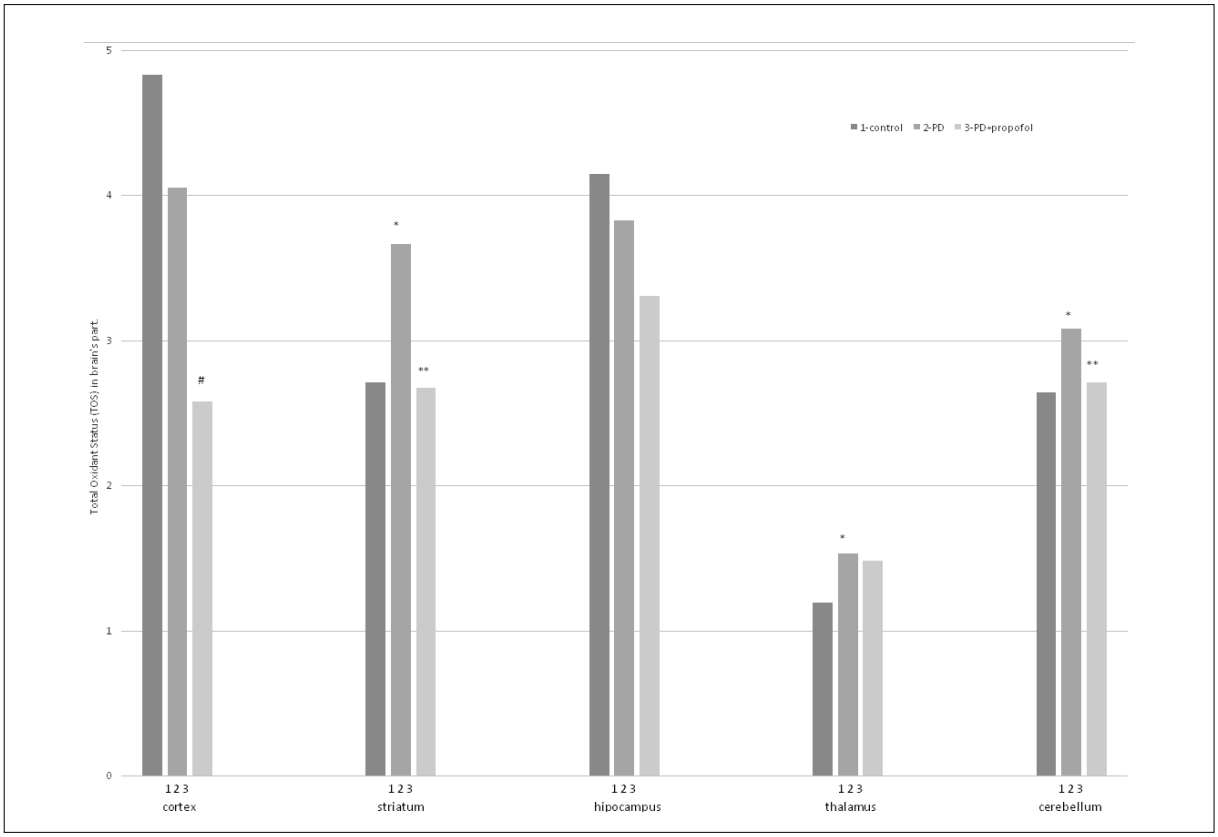

Fig. 2. Total Oxidant Status (TOS) in brain's part of the control group, Parkinson's disease group and Parkinson's disease group after administration of propofol. * 1*vs*2 - p<0.05; ** 2*vs*3 - p<0.05; #2*vs*3 - p<0.001

with the control group and increased in the striatum. In the Parkinson's disease group with propofol (group 3) we observed a statistically significant decrease in Cu/ZnSOD activity in the cortex and striatum and a statistically significant increase in the thalamus compared with the Parkinson's disease rats without propofol (group 2) (Figure 3, 4, 5)

Malondialdehyde concentration significantly increased in the striatum, hippocampus and thalamus of Parkinson's disease rats (group 2) compared with the control group and decreased in the cortex, striatum, hippocampus and thalamus in Parkinson's disease rats with administered propofol (group 3) compared to the Parkinson's disease rats without propofol (group 2) (Figure 6).

Discussion

The increasing number of surgical procedures in patients with PD supports the search for drugs that can protect tissues from the adverse consequences of oxidative stress [28]. The surgical procedures disrupt the antioxidant mechanisms of the body and increase the generation of free radicals [25], and therefore anaesthetics with an antioxidant component may be particularly useful. It is essential for the administered drug to be characterized by a high lipophilicity, the ability to penetrate the blood-brain barrier, and a relatively low molecular weight and charge density [21]. Thus molecules with the required pharmacokinetic and pharmacodynamic properties are constantly being sought. Propofol has all these properties, and is also characterized by strong antioxidant properties that have been confirmed in various models of oxidative stress [12,16,20,24], but the effect of propofol on specific areas of the brain under oxidative stress which is observed in PD has not been tested. Our study is the first to evaluate whether propofol can have a significant effect on oxidative stress and strengthen the antioxidant defence in the areas of the brain relevant to PD, including the striatum, cerebral cortex, thalamus, cerebellum, and hippocampus, in a rat model of PD.

The most important enzymes that regulate the level of superoxide anion radical ($O_2^{\cdot-}$) in the brain are SODs, including cytoplasmic isoenzyme, identified by the prosthetic group of zinc and copper ions (Cu/ZnSOD) and mitochondrial isoenzyme with a prosthetic group in the form of manganese ions (MnSOD). SODs are a family of enzymes that catalyse the reaction of dismutation of superoxide anion of hydrogen peroxide and oxygen [13]. The antioxidant system of SOD and its isoenzymes MnSOD and Cu/ZnSOD protects the brain against oxidants. Due to the high reactivity of $O_2^{\cdot-}$, maintaining the activity of SODs at an appropriate level is necessary for normal cell functioning [13,34]. Significant progress in understanding the structure and the location of SODs and a growing awareness of the role that may be played by these enzymes encourages assessment

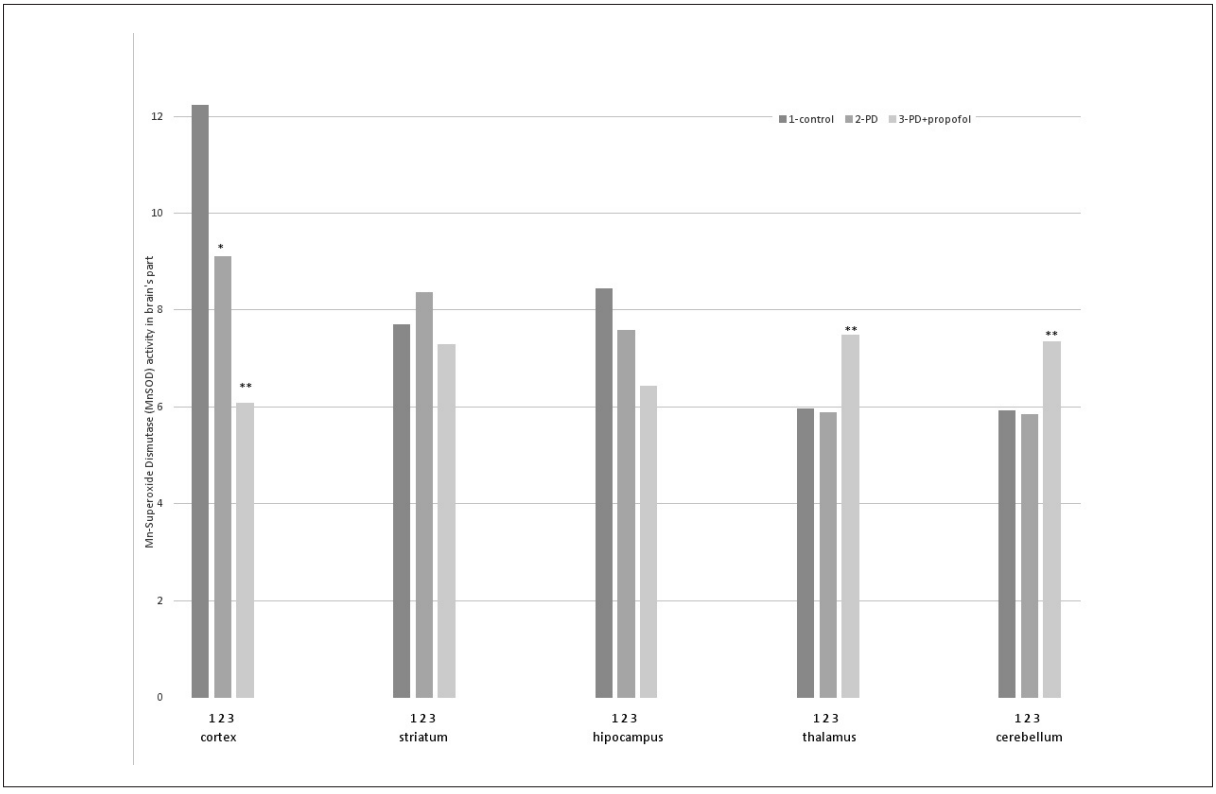

Fig. 3. Mn-Superoxide Dismutase (Mn-SOD) activity in brain's part of the control group, Parkinson's disease group and Parkinson's disease group after administration of propofol. *1*vs*2 - $p<0.05$; ** 2*vs*3 - $p<0.05$; #2*vs*3 - $p<0.001$

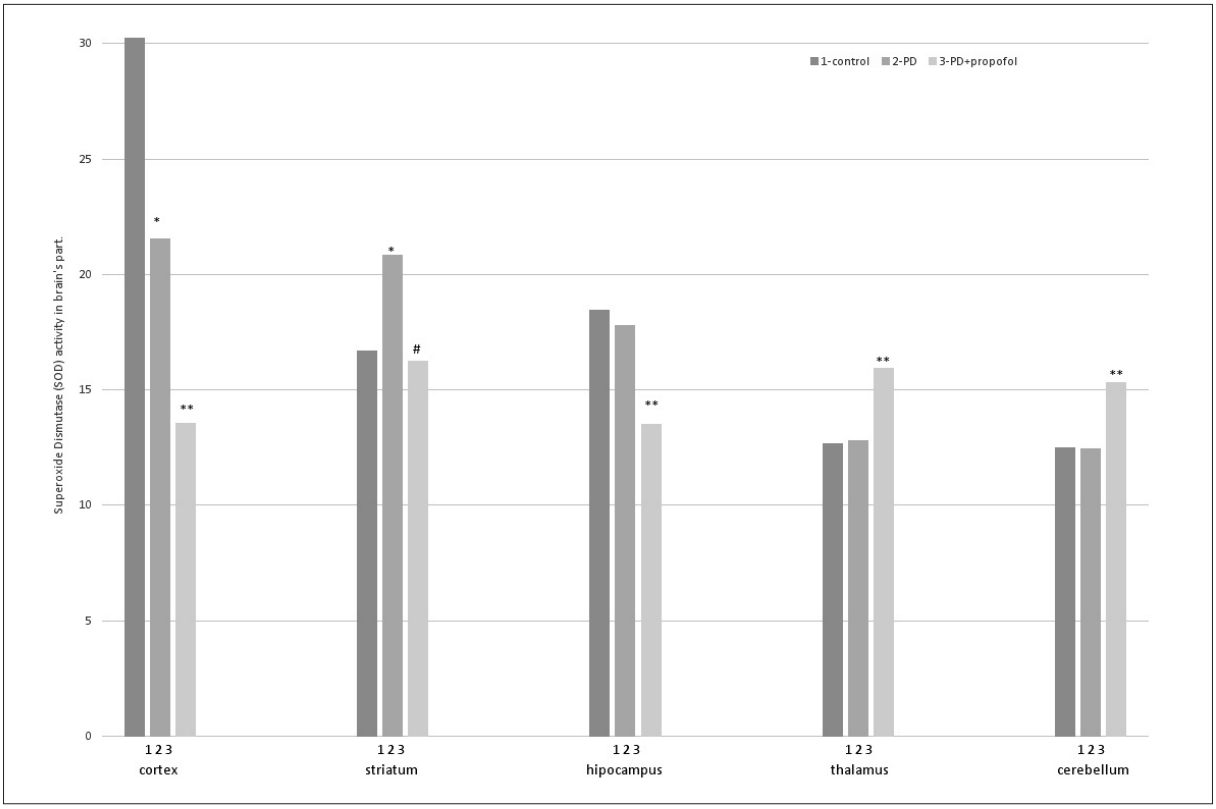

Fig. 4. Superoxide Dismutase (SOD) activity in brain's part of the control group, Parkinson's disease group and Parkinson's disease group after administration of propofol. * 1*vs*2 - p<0.05; ** 2*vs*3 - p<0.05; #2*vs*3 - p<0.001

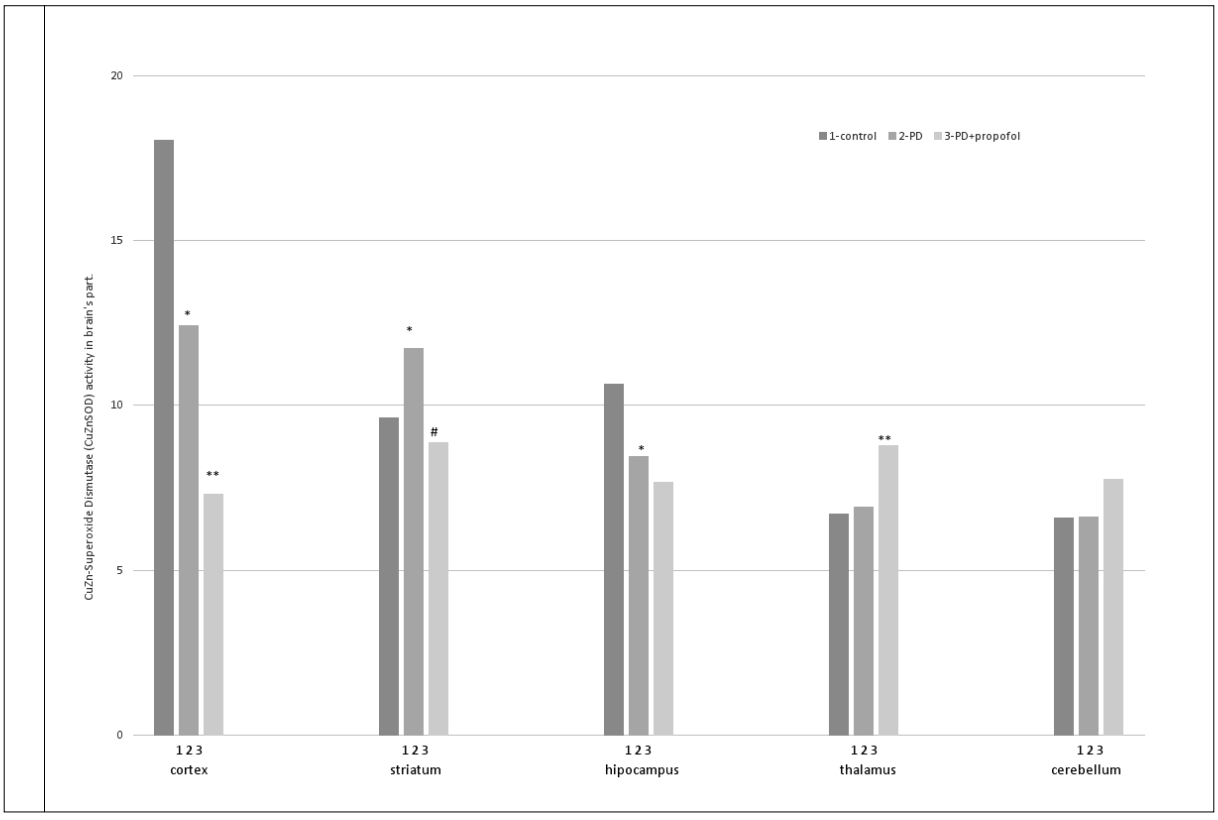

Fig. 5. CuZn-Superoxide Dismutase (CuZn-SOD) activity in brain's part of the control group, Parkinson's disease group and Parkinson's disease group after administration of propofol. * 1*vs*2 - p<0.05; ** 2*vs*3 - p<0.05; #2*vs*3 - p<0.001

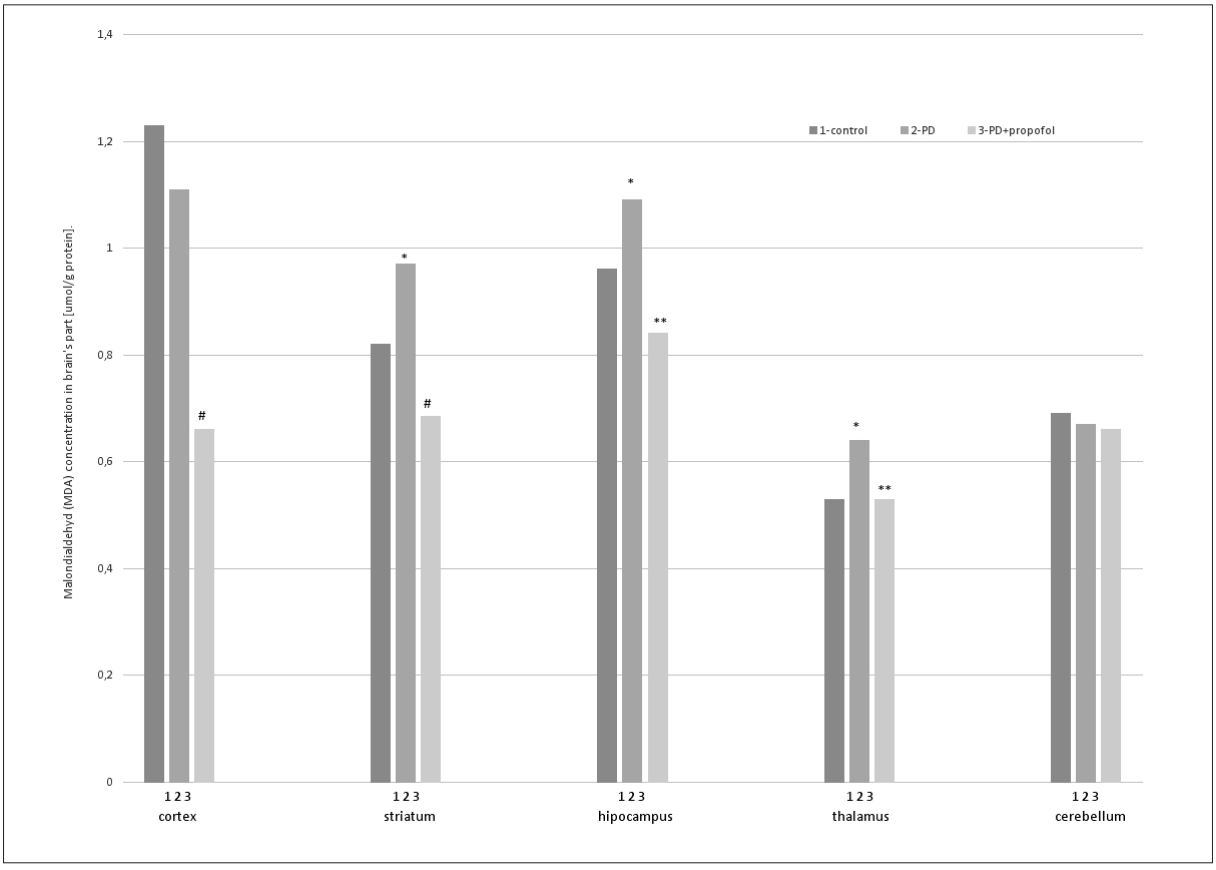

Fig. 6. Malondialdehyde (MDA) concentration in brain's part of the control group, Parkinson's disease group and Parkinson's disease group after administration of propofol. *1*vs*2 - p<0,05; ** 2*vs*3 - p<0.05; #2*vs*3 - p<0.001

of the role that they can play in different brain structures. There is general agreement that SOD and its isoenzymes are critical to antioxidant defence in the brain [26]. Studies also indicate that the failure of the activity of SOD and its isoenzymes may play a significant role in the severity of oxidative damage in the brain in PD [26,33]. The assessment of the activity of SOD and its isoenzymes in PD and the effect of propofol on SOD activity is justified due to the wide range of effects of these enzymes and their significant impact on the protection of cells against reactive oxygen species in both cytoplasmic and mitochondrial compartments. Our research has shown that the activity of SOD and its isoenzymes undergoes a significant depletion in the cerebral cortex in PD rats, in comparison to a group of healthy subjects, whereas the administration of propofol causes an even stronger decrease in the activity of these enzymes. A significant reduction in the activity of Cu/ZnSOD in the hippocampus in the group of PD rats is observed, as compared to the control group. There is no change in activity of this enzyme after propofol administration in PD rats. However, the activity of SOD and Cu/ZnSOD in the striatum increased greatly. One possible response of the cell to stress is increasing the expression of the SOD gene, which allows stimulation of superoxide dismutase activity in the areas that are most vulnerable to damage caused by free radicals [11]. It is possible that this is a compensation mechanism in response to a significant increase in ROS production in the area pathognomonic for PD, where the production of free radicals is increased the most. In our study the administration of propofol in rats with PD resets SOD activity to the level observed in healthy subjects. It is likely that propofol directly neutralizes free radicals, which reduces the level of ROS, and thus the enzyme activity is normalized. There was no change in SOD activity in the thalamus in PD rats, as compared to the control group, while the administration of propofol caused significant stimulation of the activity of SOD and its two isoenzymes. A similar situation was observed in the cerebellum of PD rats. No changes were observed in the activity of SODs, while after the administration of propofol in PD rats the activity of SOD and MnSOD significantly increased. Propofol has a positive effect on the level of SOD-dependent enzyme activity in the striatum, cerebellum and thalamus. These differences between the activity of SOD and its isoenzymes in specific areas can be explained by the local significance of each enzyme in each cell compartment. Thus, the activity of antioxidant enzymes is specific for a given area.

Evaluation of the overall oxidative stress causes a lot of problems, because of the wide panel of natural antioxidant enzymes, non-enzymatic free radical scavengers

and the diversity of the presence of ROS. In addition, separate measurements of individual antioxidant enzymes and different oxidant and antioxidant molecules are laborious and expensive, because of the wide range of parameters of the oxidant-antioxidant system. This greatly impedes the evaluation of the total oxidant-antioxidant balance. Thus, in order to assess the global oxidative stress in the tissue, the parameter of total oxidative status (TOS), which encompasses a broad range of oxidants involved in damaging the cells, may be more helpful. On the other hand, the evaluation of the antioxidant status with the non-enzymatic component can be done by measuring the total antioxidant capacity (TAC). The analysis of parameters including TAC and TOS allows complete evaluation of tissue exposure to oxidative stress [3,5,6]. Antioxidant systems act as a whole by neutralizing continuously generated free radicals. Thus, the overall rating of this system is extremely important for understanding the nature of the changes in the course of PD and assessing the effects of drugs on the overall balance of the oxidant-antioxidant system. Our study showed that in rats with PD there is a significant reduction in TAC in all areas of the brain, except the cerebellum, as compared to the corresponding control group. However, after the administration of propofol to the subjects with PD, a significant increase in the concentration of the TAC in all the analysed structures was observed. This shows that propofol can significantly increase the pool of antioxidants in the brain and thus increase the defences against ROS.

In all the analysed structures of the brain, with the exception of the cerebral cortex and hippocampus, there was a significant rise of oxidative stress, as evidenced by a significant increase in the concentration of TOS in the group of PD rats as compared to the control group. This shows that in the course of PD, the pool of free radicals is increased. What is important, free radicals can interact with endogenous molecules, causing oxidative damage and altering cell function. Physiological disorders of the cellular redox state in neurons can ultimately lead to destruction of the cells [30]. Other studies also support the theory of increased oxidative stress in PD [2,8], but our study is the only one which shows that these changes are present in many brain structures simultaneously. One of the possible theories that explain covering such a large area of the brain in PD is the existence of functional connections between the various areas of the brain. It seems that the presence of degenerative changes in one area may impair the functioning of any other area of the brain [7]. Administration of propofol in rats with PD causes a significant reduction of TOS in the cerebral cortex, striatum and cerebellum, which indicates that propofol can protect some brain areas from the damaging potential of free radicals.

Neurons are particularly sensitive to the damaging effect of ROS and the oxidation of polyunsaturated fatty acids, due to the high lipid content in cell membranes and intensive oxygen metabolism in the brain. The proper conduction of nerve impulses depends on the smooth functioning of the cell membrane [8]. Thus, the increase in oxidation of polyunsaturated fatty acids leads to the disintegration of cell membranes and disturbances in the normal functioning of the cell and the conduction of nerve impulses. Lipid peroxidation processes take place rapidly, which means that the reaction initiated within one molecule leads to the use of a large pool of unsaturated fatty acids [1]. The products of lipid peroxidation modify the physical properties of cell membranes, causing changes in the structure of the membrane. This leads to an increase in the permeability of a membrane for polar substances and reduces the electrical potential difference on both sides of the lipid bilayer of the cell membranes. Lipid peroxidation also causes the inhibition of certain membrane enzymes and transport proteins and, consequently, the destruction of the cells [22,32]. Intermediate products of lipid peroxidation are widely used as markers of cellular oxidative damage. One of the widely evaluated and sensitive indicators of lipid peroxidation of cell membranes is MDA [1]. Our study showed that the concentration of MDA was significantly higher in the striatum, hippocampus and thalamus in rats with PD, as compared to the control group, which demonstrates the intensity of lipid peroxidation. The administration of propofol reduces the concentration of MDA in all the analysed brain structures of the sick rats, except for the cerebellum. Thus, in the course of PD, lipid peroxidation processes are increased, which impairs the proper functioning of neurons, while propofol inhibits this process, and therefore has a neuroprotective effect [12,16]. Propofol can prevent lipid peroxidation by stabilizing the lipid peroxyl radicals. The inhibitory effect of drugs on lipid peroxidation may have significant advantages in clinical practice, due to the possibility of counteracting untimely destruction of the cells and maintaining their normal functioning [10,16].

Antioxidant drugs or other compounds that increase endogenous reserves of non-enzymatic and enzymatic tissue should be an essential direction for further research to improve the effectiveness of the treatment of patients with PD. In the future, tissue antioxidant systems' modulation may become one of the elements of treating PD. We need further studies to evaluate the efficacy of propofol in long-term observation.

Conclusions

Our study confirms that oxidative stress is present in PD, but this is also the first study that separately analyses the various areas of the brain that can be damaged in PD. Our results showed that propofol increases the antioxidant defence systems in rat brain. The effects can be beneficial for patients with PD in whom free radicals play an important role. Propofol has an

antioxidant effect and it also effectively inhibits lipid peroxidation and has a positive effect on the reduction of oxidative biomarkers. The efficacy of propofol in reducing the oxidative stress level seems to result from its ability to directly scavenge ROS and the ability to stimulate the activity of natural antioxidants. Thus, propofol may have a neuroprotective effect in many areas of the brain, which may be particularly important in PD, due to the complex nature of its symptoms and the increasingly widespread view that PD does not just affect the original location of the disease – the substantia nigra of the midbrain – but also affects other areas of the brain, reflecting the complex clinical nature of PD.

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