ORIGINAL PAPERS

Adv Clin Exp Med 2016, **25**, 5, 815–820 DOI: 10.17219/acem/36459

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Effects of Propofol on the Liver Oxidative-Antioxidant Balance in a Rat Model of Parkinson's Disease

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

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Abstract

Background. Parkinson's disease is caused by the destruction of dopaminergic neurons in the substantia nigra of the midbrain. One of the possible factors involved in the pathogenesis of Parkinson's disease is impaired oxidative-antioxidative balance.

Objectives. The present study aimed to evaluate selected parameters of the liver oxidative-antioxidative system in a Wistar rat model with Parkinson's disease treated with propofol.

Material and Methods. Experiments were performed on 32 rats divided into 4 groups: 1 – control, 2 – Parkinson's disease, 3 – control with propofol, 4 – Parkinson's disease with propofol. The rats were decapitated at 8 weeks of age and their livers were collected. In the liver, the activities of catalase (CAT), glutathione peroxidase (GPx), glutathione transferase (GST), glutathione reductase (GR) and the concentrations of: Malondialdehyde (MDA), total antioxidant capacity (TAC), total oxidant status (TOS) were assessed.

Results. The study demonstrated a decrease in CAT activity and an increase in MDA, TOS concentrations in group 2 compared to that of group 1. Administration of propofol in rats of group 4 caused an increase in CAT activity and a decrease in MDA concentration compared to that of group 2 and an increase in TAC, CAT, GR levels, decrease in MDA levels compared to that of group 1. There was also an increase in GR and TAC in group 3 compared to that of group 1.

Conclusions. Propofol in Parkinson's disease stimulates the production of antioxidant enzymes in the liver, simultaneously decreasing oxidative stress, which has a beneficial effect on the oxidative-antioxidative balance (Adv Clin Exp Med 2016, 25, 5, 815–820).

Key words: oxidative stress, rats, Parkinson's disease, propofol, antioxidant effects.

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder affecting 1% of the population over the age of 55, and the risk of PD is significantly increased in the elderly [1]. As PD progresses, dopaminergic neurons in the substantia nigra of the midbrain are lost as a result of the progressive degenerative process revealed by a reduction in dopamine levels in this structure [2]. Despite years of research, the pathogenesis of PD is not fully understood, although many factors are thought to be involved. One hypothesis is that PD is caused by increased oxidative stress. Roles for the oxidation-oxidant system in other disorders have been confirmed by numerous studies demonstrat-

ing potentiation of lipid peroxidation, reduction in the concentrations of reduced glutathione and antioxidant enzyme activity, increased malondialdehyde concentration, and disruption of iron metabolism. Environmental toxins and genetic disorders associated with apoptosis and protein breakdown may also play a role [2, 3]. Oxidative stress leads to the damage of extremely sensitive neurons and is an important factor in both the initiation and progression of PD. This damage is revealed by increases in either the oxidation or reduction activity of enzymes with antioxidant activity. These changes to the oxidation-antioxidant system may also simultaneously affect both oxidation and reduction

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processes [4]. In light of these reports, it seems reasonable to search for new substances that can be used to remove free radicals and induce antioxidant system activity. Such a substance may be used to help prevent PD or to supplement existing treatments. Propofol (2,6-diisopropylphenol) displays the aforementioned characteristics and is used in anesthesia. In addition to its primary use in general anesthesia, propofol appears to exert a number of other pleiotropic effects, of which its antioxidant properties are particularly noteworthy. These effects arise from its chemical structure, as it contains propofol phenolic groups that are capable of removing free radicals and inhibiting lipid peroxidation, similar to the action of the endogenous antioxidant alpha-tocopherol [5]. The listed properties of propofol suggest that it may have protective effects that are relevant to neurodegenerative disease. Accounting for the special role of oxidative stress in the pathogenesis of PD, it has been suggested that future treatments will include antioxidant therapy [3, 6]. The present study aimed to evaluate selected parameters of the liver oxidativeantioxidative system in a Wistar rat model of Parkinson's disease treated with propofol.

Material and Methods

Animals

The experiment was performed using 32 male Wistar rats weighing 180–200 g. The animals were housed in standard conditions: 55–60% moisture at a temperature of 21–22°C, with a 12 h/12 h day/night cycle and unlimited access to food and filtered water. This experiment was approved by the Local Ethics Committee of the Medical University of Silesia in Katowice (permit number 33/2013).

Experimental Model of Parkinson's Disease

To model PD, 6-hydroxydopamine (6-OH-DA) was administered intraventricularly to neonatal rats to destroy the central dopaminergic system. This damage is maintained over the animal's lifespan [7]. Newborn Wistar rats were separated into two groups and treated as follows: Group 1 – 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, followed by intraventricular (i.c.v.) administration of 10 μ L 0.1% ascorbic acid solution 60 min later. Group 2 – rats with central dopaminergic system lesions. Desmethylimipramine was administered to 3-day-old animals (20 mg/kg body weight

in a 1.0 mL/kg body weight volume by IP) followed by administration of 15 μ g 6-hydroxydopamine (6-OHDA) in 5 μ L 0.1% ascorbic acid solution into each lateral ventricle of the brain 60 min later.

Experimental Design

Animals were housed with their mothers until 4 weeks of age, and then segregated by sex and placed in separate cages. The experiment was performed using 32 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 lesions affecting the central dopaminergic system treated with 1.0 mL/kg body weight 0.9% NaCl solution *ip.* Group 3 – control rats treated with 60 mg/kg body weight propofol IP. Group 4 – rats with lesions affecting the central dopaminergic system treated with 60 mg/kg body weight propofol ip. Administration of propofol and 0.9% NaCl was performed once, 60 min prior to decapitation.

Decapitation and Preparation of Livers for Analysis

Animals were sacrificed by decapitation for organ harvest at 8 weeks of age. The dissected organs were suspended in a 0.9% NaCl solution. Prepared tissues were then frozen at -80°C and stored for further biochemical studies, and oxidative-antioxidant parameters were determined using homogenized prepared liver tissue.

Biochemical Assays

We assayed catalase (CAT) activity using the kinetic method described by Aebi [8], glutathione reductase (GR) activity using the modified semi-automatic method described by Richterich [9], glutathione peroxidase (GPx) activity as described by Paglia and Valentine [10], glutathione S-transferase (GST) activity using the kinetic method described by Habig [11], and measured the total antioxidant capacity (TAC) as described by Erel [12]. Oxidative system activity was assessed by determining the total oxidant status (TOS) as described by Erel [13], and the concentration of malondialdehyde (MDA) was measured as described by Ohkawa [14]. Total protein concentration of liver homogenate was measured as described by Lowry [15].

Statistical Analysis

Statistical analysis was performed using STA-TISTICA v. 10. The Kolmogorov-Smirnov test was used to verify that the data was normally distribut-

ed, whereas Levene's test was used to verify the homogeneity of variances. Normally distributed data was described as a mean and standard deviation (SD). For the comparative analysis of all studied groups, we have used one-way ANOVA test and *post-hoc* tests. Due to the small size of the groups we have also used non-parametric Kruskal-Wallis and *post-hoc* Kruskal-Wallis test, which confirmed the results obtained from the use of parametric tests. The value of p < 0.05 was considered to be statistically significant.

Results

During our experiment we have observed statistically significant changes in oxidant-antioxidant status examined in the liver of Parkinson's rats (Table 1).

Catalase activity was reduced in a statistically significant way in Parkinson's rats (group 2) compared to the healthy control group (group 1). But a statistically significant increase was observed in catalase activity in Parkinson's rats treated with propofol (group 3) compared together to the healthy control group (group 1), healthy control group treated with propofol (group 3) and to the Parkinson's rats without propofol treatment (group 4).

Administration of propofol both in Parkinson's rats (group 4) and in healthy control group

(group 3) has caused an increase in glutathione reductase activity compared to the healthy control rats without propofol administration (group 1).

There were no changes in the activity of other glutathione-dependent enzymes – glutathione transferase and glutathione peroxidase.

We have observed a statistically significant increase in TAC in Parkinson's rats treated with propofol (group 4) compared to the control group without propofol administration (group 1) and in a control healthy group treated with propofol (group 3) compared to the control group without propofol administration (group 1).

TOS was raised in a statistically significant way in the Parkinson's rats (group 2) compared to the healthy control group (group 1).

Product of lipid peroxidation – MDA was higher in statistically significantly manner in Parkinson's disease group (group 2) than in the healthy control group (group 1), and we have observed a statistically significant decrease in MDA concentration in Parkinson's rats treated with propofol (group 4) compared to the healthy control group (group 1) and also compared to the Parkinson's rats without propofol administration (group 2) and to the control with propofol administration (group 3).

Using one-way ANOVA, we found differences in the catalase activity (p < 0.05) and MDA concentration (p < 0.05) between the four studied groups.

Table 1. Oxidative-antioxidant parameters in the livers of studied	rats
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	Control group 1	6-OHDA group 2	Control + propofol group 3	6-OHDA + propofol group 4
GR IU/g protein	20.77 ± 2.67	22.67 ± 5.79	$26.75 \pm 2.08^{\ 1)}$	25.71 ± 4.09 ¹⁾
CAT kIU/g protein	1020.71 ± 125.17	766.17 ± 142.89 ³⁾	1143.65 ± 270.95	$1562.27 \pm 275.13^{\ 2)\ 4)$
GPX IU/g protein	285.50 ± 84.16	317.0801 ± 70.15	272.32 ± 91.29	324.47 ± 98.94
GST IU/g protein	13.19 ± 1.57	12.72 ± 2.38	13.92 ± 1.12	14.12 ± 2.87
TAC μmol/g protein	0.12 ± 0.03	0.1343 ± 0.03	$0.162 \pm 0.02^{\ 1)}$	0.157 ± 0.02^{3}
TOS μmol/g protein	0.334 ± 0.05	$0.364 \pm 0.04^{1)}$	0.314 ± 0.08	0.227 ± 0.05 ¹⁾
MDA μmol/g protein	3.78 ± 1.40	7.01 ± 1.61 ³⁾	3.54 ± 1.75	2.03 ± 0.43 ^{1) 4) 5)}

 $^{^{1)}}$ p < 0.05 compared to the control group;

²⁾ p < 0.001 compared to the control group and 6-OHDA group;

 $^{^{3)}}$ p < 0.001 compared to the control group;

⁴⁾ p < 0.05 compared to the control + propofol group;

 $^{^{5)}}$ p < 0.001 compared to the 6-OHDA group.

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Discussion

Under physiological conditions, there is a balance between the production and removal of reactive oxygen species. Increased production of free radicals or an impaired antioxidant defense system disturbs the normal oxidative-antioxidative balance, resulting in an imbalance favoring oxidation processes. Numerous studies have confirmed the role of oxidative stress in the pathologies of neurodegenerative diseases, including PD [3, 4, 16, 17]. The immediate manifestation of severe free radical processes is an increase in MDA concentration, an important lipid peroxidation indicator that reflects the extent of tissue destruction [18]. It has been suggested that the levels of specific markers for lipid peroxidation may be used as prognostic factors for patients with neurodegenerative diseases [17]. Study by Buhmann et al. also supports the idea that increased oxidative stress plays a role in the pathology of the neurodegenerative disorders [19]. Additionally, Kirbas et al. evaluated the condition of potential oxidation-antioxidant in serum by measuring the TAC, constituting the antioxidative component, and the TOS, which reflects the intensity of free radical processes. The authors of this study have demonstrated that patients with Parkinson's disease display a significant increase in TOS and a significant decrease in TAC compared to the control group [20]. In our study, the severity of the adverse oxidative effects was demonstrated by noting increases in liver MDA concentration and TOS, and a significant reduction in catalase activity in rats with PD (group 2) compared to the control group (group 1). Stress oxidative was observed in the liver of rats with PD. Together, the results of earlier work and the present study demonstrate that the observed oxidation-antioxidant balance disorders are both central and peripheral, implicating systemic oxidative stress in PD. Consequently, it is reasonable to search for substances whose scope of action is not limited to neuroprotective effects on the central nervous system but also includes beneficial effects on the oxidation-antioxidant balance of peripheral tissues. It seems that propofol displays these properties and its antioxidant activity can be explained, inter alia, by the presence of a phenolic group with the capacity to scavenge free radicals [5]. However, the effects of propofol on liver hepatocytes under conditions of increased oxidative stress are not fully understood. To address this knowledge gap, our research has focused on assessing the impact of propofol on the liver oxidative-antioxidative system that plays a key role in maintaining organism homeostasis, and this balance is disturbed in the course of many diseases. In our study, we observed a significantly higher catalase activity in a group of rats with lesions in the dopaminergic nervous system that were treated with propofol (group 4) compared to rats with PD (group 2). Catalase is an antioxidant enzyme that catalyzes the decomposition of hydrogen peroxide into water and oxygen, thereby preventing the production of a hydroxyl radical from H₂O₂ through a Fenton reaction. Consequently, catalase activity prevents the formation of a more reactive oxygen species that could induce neuron cell membrane failure and DNA damage [21]. Our studies also show that the administration of propofol to PD rats (group 4) inhibited lipid peroxidation, demonstrated by significantly lower MDA concentrations compared to the PD group (group 2). Several studies have examined the effects of propofol on the oxidation-antioxidant balance in peripheral tissues; however, there is no data evaluating the effect of this drug on the above system in Parkinson's disease. A study by Ranjbar et al. demonstrated that the administration of propofol to rats that had been exposed to oxidative stress induced by carbon tetrachloride (CCl4) stimulated liver antioxidant capacity to inhibit the formation of free radicals, thereby protecting the cells from increased oxidative stress damage [22]. Wang et al. also showed that propofol protects liver cells under conditions of increased oxidative stress [23]. These advantageous properties of propofol can be explained by its ability to scavenge free radicals, leading to decreased lipid peroxide formation and induction of antioxidant enzymes.

Although the data is unclear, several recent articles have drawn attention to the influence of other substances on oxidative stress levels in PD. Using the cellular model of PD, Strathearn et al. demonstrated that substances that are rich in anthocyanins might protect neurons from degeneration [24]. Sikorska et al. documented similar observations regarding the beneficial effects of antioxidants on the inhibition of neurodegenerative processes [25]. Additionally, other studies have indicated that the consumption of large amounts of vitamin E may protect against the development of PD [26]; however, a study by Weber et al. [27] does not prove the benefits of this vitamin. Furthermore, Etminan et al. conducted a meta-analysis of eight studies and did not provide conclusive results regarding the efficacy of natural antioxidants in PD; however, the authors suggested that administration of vitamin E could have neuroprotective effects, thereby reducing the risk of disease [28]. The literature contains many contradictions regarding the efficacy of antioxidants in the treatment of PD. In vivo, these discrepancies may arise from a selection of the group by age of onset, severity of illness, duration of therapy. Additionally, the properties of the administered substances can significantly affect the results.

Our research also indicates that propofol is beneficial to the antioxidant system of healthy rats. Healthy individuals treated with propofol (group 3) had increased glutathione reductase activity and significantly increased TAC compared to the healthy group that did not receive propofol (group 1). Concomitant with these effects, there were no significant changes to MDA, TOS or catalase activity levels. Glutathione reductase catalyzes the reaction of reduced glutathione (GSH) in the presence of nicotinamide-adenine dinucleotide, and an increased pool of reduced glutathione protects the protein sulfhydryl groups prior to oxidation and serves as a reservoir capable of inactivating cellular free radicals [21, 29]. Our results are consistent with a study by Adaramoye et al. [30]. The present authors demonstrated an increase in the levels of reduced glutathione and the GSH-dependent enzyme in the liver of rats treated with propofol, but did not observe any changes to MDA concentration of catalase activity [30]. Our study shows that the administration of propofol to healthy individuals does not lead to any significant changes in oxidative system activity, thereby providing valuable information regarding the safety of this drug. Furthermore, under conditions of severe oxidative stress, propofol was able to scavenge free radicals to inhibit lipid peroxidation, and thus inhibiting adverse pro-oxidant processes. It seems that in the case of increased oxidative stress observed in PD, administration of propofol leads to the induction of additional mechanisms responsible for the defense of the organism against increased generation of free radicals; however, the antioxidant properties of propofol are not fully understood. Undoubtedly, the chemical structure of propofol confers an ability to capture and neutralize free radicals, but it does not explain the possible stimulation of the activity of other antioxidants. In this study we have shown that propofol increases antioxidant enzyme activity in both healthy rats (group 3) and those with central dopaminergic lesions (group 4); however, it is interesting to note that propofol acts more favorably under conditions of increased oxidative stress. Comparative analysis of the groups showed a statistically significant elevation of catalase activity and reduction

of MDA concentration for the PD group treated with propofol (group 4) as compared to healthy rats receiving the same drug (group 3). Oxidative stress appears to play an important role in the pathology of neurodegenerative disorders. Our research shows that in a rat model of PD, there is significant severe oxidative stress that is revealed by the severity of lipid peroxidation, TOS increase and catalase activity decrease. Under such conditions, propofol is capable of neutralizing free radicals and strongly stimulating the body's antioxidative system to fight ROS. Comparing PD rats receiving propofol (group 4) to the control group (group 1), we observed lower MDA concentration, much higher catalase and glutathione reductase activities together with increased TAC in the diseased rats treated with propofol. We showed an increase in TOS in the group of PD rats treated with propofol (group 4) compared to the control group (group 1), but the results were not statistically significant. Additionally, we showed that the concentration of TOS in the group 4 is comparable to the TOS concentration in the group 2, indicating that propofol does not cause oxidative stress increase. The increasing trend of TOS concentration in group 4 compared to that of group 1 is caused by increased oxidative stress in PD.

The future use of antioxidants in the treatment of PD is promising. It is possible that in the future compounds capable of scavenging free radicals and inducing antioxidant enzymes, such as propofol, will be used as a supportive therapy for the treatment of PD. Future experimental and clinical studies may increase our understanding of the role of oxidative stress in PD pathology and provide further evidence regarding the desirability of including antioxidant therapies in treatment. Further research should also be directed towards assessing the long-term efficacy of potential antioxidant substances.

In conclusion, our study suggests that the destruction of the dopaminergic nervous system leads to increased oxidative stress in the livers of rats with Parkinson's disease. This study also shows that the administration of propofol exerts a beneficial effect on the oxidative-antioxidative balance; however, this drug is more effective under conditions of increased oxidative stress than in healthy subjects.

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Received: 16.10.2014 Revised: 5.01.2015 Accepted: 14.01.2015