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Changes in Oxidative Stress Index and Lipid Peroxidation Product in the Brain of Rats with Lesion of Central Dopaminergic System after Propofol Administration*

Zmiany wskaźnika stresu oksydacyjnego i produktu peroksydacji lipidów w mózgu po podaniu propofolu u szczurów z lezją ośrodkowego układu dopaminergicznego

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

Aim: Propofol is a commonly used intravenous anesthetic agent with antioxidant properties. However, the effect of propofol on oxidative stress index (OSI) and lipid peroxidation in Parkinson's disease is still unknown. The present study aimed to evaluate the effect of propofol on OSI and malondialdehyde (MDA) level in the selected brain regions of the rats with Parkinson's disease (PD).

Material/Methods: 32 male Wistar rats were divided into four groups: I- control group, II- group with PD, III-control group with propofol, IV-PD group with propofol. 60mg/kg of propofol was given to the 8-weeks-old rats intraperitoneally, and the selected parts of the rats' brains (frontal cortex, striatum, thalamus and hippocampus) were isolated after decapitation. The concentration of MDA, which is a marker of lipid peroxidation, and OSI were measured.

Results: In group IV compared to group II, was observed a significant MDA level decrease in the cortex (39%, p <0.001), striatum (28%, p <0.001), hippocampus (21%, p <0.05) and thalamus (20%, p <0.05), together with a decreased OSI level in the thalamus (71%, p <0,001), cortex (70%, p <0.05), striatum (65%, p <0.001), and hippocampus (57%, p <0.05). In group III compared to group I was observed decrease in MDA level in the cortex (40%, p <0.001).

Conclusions: Propofol inhibits oxidative stress in all the evaluated structures of the rat brain with Parkinson's disease. There are significant differences in the response of brain tissues to administered propofol between rats with PD and healthy ones.

Keywords: oxidative stress index • malondialdehyde • Parkinson disease • propofol

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Abbreviations: **MDA** – malondialdehyde, **6-OHDA** – 6-hydroxydopamine, **PD** – Parkinson's disease, **ROS** – reactive oxygen species, **TAC** – total antioxidant capacity, **TOS** – total oxidative status, **OSI** – Oxidative Stress Index.

INTRODUCTION

Parkinson's disease (PD) is recognized as the second most common progressive neurodegenerative disease. During the disease the selective loss of the dopaminergic neurons in the *substantia nigra pars compacta* and the reduction of dopamine neurotransmitter in the striatum is observed [1]. Various factors are implicated in the pathogenesis of PD but gathered evidence indicates that the increasing generation of Reactive Oxygen Species (ROS) plays a critical role in the damage of dopaminergic neurons [7, 11, 13, 14]. Increased exposure of cells to ROS and depletion of defensive endogenous antioxidant systems leads to the increased susceptibility of cells to oxidative stress and the progressive loss of dopaminergic neurons [14]. Lipid peroxidation products in the striatum which may contribute to nigral cell death was observed in postmortem analysis of the human brain with PD [11]. Striatal oxidative stress is enhanced in patients with PD and increases with the progression of disease severity, which was confirmed by the recent PET imaging study [13]. There is a strong relationship between the accumulation of oxidative stress and dopaminergic neuronal degeneration in the striatum. But, an extensive neurodegeneration and atrophy are also observed in different regions of the patient with PD's brain, such as hippocampus, thalamus, cortex and cerebellum, contributing to the appearance of not only characteristic motor symptoms of PD, but also the non-motor symptoms [20, 25]. Increased production of free radicals in combination with deficient antioxidant enzymes, causing system-wide effects of the oxidative stress on brain functions [14, 20]. In addition, human brain is more susceptible to oxidative damage than other body tissues because of the high concentrations of polyunsaturated fatty acids, low antioxidant activity and the high level of oxygen consumption, compared to its relatively small weight [39]. Currently, there is no therapy that delays the neurodegenerative processes, in PD patients. Reduction in the generation of free radicals together with the improvement of the antioxidant reserve is one of the potential approach to improving treatment of complications during PD. Therefore, it is necessary to search for antioxidant drugs able to suppress the oxidative stress in brain cells [6, 15, 39].

Among most popular agents used for anesthesia and for the long-term sedation important place take propofol (2,6-diisopropylphenol). Phenolic structure of propofol is similar to that of α-tocopherol, and presents antioxidant properties that have been demonstrated in different models of oxidative stress [27, 32, 33, 37]. There is no study about the effect of propofol on oxidative stress index (OSI) and lipid peroxidation in various regions of the rats' with lesion of central dopaminergic system. In our study we have focused on frontal cortex, striatum, thalamus, hippocampus of rats with lesion of central dopaminergic system. In this experimental model of PD we have evaluated the effect of propofol on OSI and malondialdehyde (MDA) levels.

MATERIALS AND METHODS

Animals

Male Wistar FL rats were purchased from the Center of Experimental Medicine of the University of Silesia in Katowice, Poland. All study groups were housed and maintained in the same, controlled conditions, 22 ± 1°C, humidity 60% ± 5, and 12-hour light-dark cycles, with a free access to food and water. The procedures of the experiment were performed on newborn Wistar rats and the animals which had just reached maturity. All experimental procedures were conducted according to the ethical standards and protocols approved by the Local Ethics Committee of the Medical University of Silesia in Katowice (permit No. 33/2013) and performed in accordance with principles and guideline described in the Declaration of Helsinki. All efforts were made to minimize the number of animals and their suffering.

INDUCTION OF BRAIN LESIONS BY INJECTION OF 6-HYDROXYDOPAMINE

Newborn Wistar rats were treated as follows:

Group I: control rats. Intraperitoneally (IP) administration to 3-day-old animals of Desmethylimipramine (20 mg/kg body weight in a 1.0 ml/kg body weight vol-

ume). Next, intracerebroventricular administration of 10 µl 0.1% ascorbic acid solution were performed, after one hour.

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

To produce cold-anesthesia rat pups were immersed in ice for 60 sec and the above-mentioned substances were administered. Pups were then placed on a flat surface under a bright light. In this manner, the sagittal and transverse sinuses overlying the cranium, as well as bregma and lambda, can be seen through the transparent intact dermis. A 26-gauge needle, attached to a microliter syringe, is positioned 1.5 mm anterior to lambda and 2 mm lateral to the sagittal plane. The needle, equipped with a polyethylene sleeve up to 2 mm from the tip, is then lowered to the stop position (i.e., sleeve), with the needle in the lateral ventricle. After injection of 5 ml of 6-OHDA or vehicle, the needle is left in place for at least 30 sec. Immediately afterward, an injection is made in the same manner into the other lateral ventricle. This procedure produces no lethality and does not shorten the life span, while rat pups continue to suckle through the pre-weaning period; and eat without impairment post-weaning. For details, see Kostrzewa et al [17, 18].

6-OHDA which applied to the lateral ventricles of the brain causes a persistent, near-total destruction of nigrostriatal dopaminergic fibers and profund reduction in adulthood levels of striatal dopamine (99%), 3,4-dihydroxyphenylacetic acid (99%) and homovanillic acid (99%). Nonlethality of the procedure, reproducibility of effects and neuroanatomical and neurochemical outcomes were the factors that contributed to the rats lesioned shortly after birth with 6-OHDA have been proposed to be a model of severe Parkinson's disease [17, 18].

EXPERIMENTAL MODEL

Rat pups remained with their mothers until the 28th day of age.For the remainder of the experiment, 32 Wistar rats (180-200 g) were divided into groups of 8 as follows:

Group 1 – healthy rats – control group – received 1.0 ml/kg body weight 0.9% NaCl solution.

Group 2 – rats with lesion of central dopaminergic system(PD model) – treated with 1.0 ml/kg body weight 0.9% NaCl solution.

Group 3 – healthy rats – control with propofol – treated with 60 mg/kg body weight propofol.

Group 4 – rats with lesion of central dopaminergic system (PD model) with propofol administration – received 60 mg/kg body weight propofol.

Administration of propofol and 0.9% NaCl solution was performed treated once. These substances were administered intraperitoneally, 60 minutes prior to the decapitation of the animals.

Rats were decapitated at 8 weeks and brains were immediately excised and placed on the ice. Separation of the frontal cortex, striatum, thalamus, hippocampus and cerebellum were done at a temperature of 0°C, placed on dry ice, weighed, and stored at -70°C, pending further analysis. Tissue samples from each organ were homogenised on ice by using an UP50H ultrasonic processor (Hielscher). The homogenates were centrifuged at 3000 rpm for 10 minutes, and supernatant was used for assay of the oxidant-antioxidant parameters.

BIOCHEMICAL ANALYSIS

Protein determination

Protein concentration was determined by Lowry methods using bovine serum albumin as the standard [26].

Lipid peroxidation product

Malondialdehyde (MDA) concentration in brain tissue samples was measured using the reaction with thiobarbituric acid according to the Ohkawa et al. method [31]. LS45 spectrofluorimeter PerkinElmer was used for the reading at a wave length of 515 nm (absorbance) and 522 nm (emission). MDA concentration was calculated from the standard curve, prepared from 1,1,3,3- tetraethoxypropane. MDA concentration was expressed in µmol/g protein. The inter- and intra-assay coefficients of variations (CV) were 2.1% and 8.3%, respectively.

Oxidative Status Index (OSI)

Oxidative Stress Index (OSI), as a marker of oxidative stress was expressed as combined ratio of total oxidant status (TOS) to total antioxidant capacity (TAC) in arbitrary units.

The OSI was calculated according to the following formula: OSI = [(TOS, µmol/g of protein)/(TAC, µmol/g of protein) x100] [1].

Total Oxidant Status (TOS)

Total Oxidant Status (TOS) in brain tissue samples was measured by the spectrophotometrical method developed by Erel [8]. In this method oxidizing materials, contained in the sample lead to the oxidation of Fe^{2+} ions to form Fe^{3+}. The reaction proceeds in acidic

environment and consists of measuring the colour intensity of Fe^{3+} ions complexes with xylenol orange. Measurement of the color intensity spectrophotometrically is associated with the total amount of oxidant molecules that are present in the sample. The measurements were performed using EM280 biochemical analyser. The concentration of TOS was expressed in μmol/g protein. The inter- and intra-assay coefficients of variations (CV) were 2.2% and 6.4%, respectively.

Total Antioxidant Capacity (TAC)

Total Antioxidant Capacity (TAC) in brain tissue samples was measured by the spectrophotometrical method developed by Erel [9]. The most widely used colorimetric methods are 2,2-azinobis(3-ethylbenzo-thiazoline-6-sulfonate) (ABTS+)-based methods. In this method a colorless molecule, reduced ABTS, is oxidized to a blue-green $ABTS^{\cdot+}$. After mixing the colored $ABTS^{\cdot+}$ with any substance that can be oxidized, it is reduced to its original colorless ABTS form again and the reacted substance is oxidized. TAC was expressed in μmol/g protein. The inter- and intra-assay coefficients of variations (CV) were 2.8% and 6.9%, respectively.

STATISTICAL ANALYSIS

All statistical analyses were done with the "STATISTICA 10"software (Statsoft Inc., Tulsa, USA). The normality of the results distribution was verified using the Kolmogorov–Smirnov test whereas Levene's test was used to verify homogeneity of variances. Data were analyzed using non-parametric Mann-Whitney U test and they were presented as median with the first and fourth quartiles. The significance criterion was the values of $p < 0.05$.

RESULTS

A statistically significant decrease in OSI level were observed in all analyzed structures of rats brain rats with lesion of central dopaminergic system (PD model) after administration of propofol (group 4) compared with rats with lesion of central dopaminergic system (PD model) (group 2). The relative response of tissues brain to the administration of propofol was as follow: thalamus >cortex > striatum> hippocampus 71%, 70%, 65%, 57%, respectively) (Table 1).

We haven't observed any statistically significant changes when compared OSI level between healthy rats without propofol administration and healthy rats with propofol administration (Table 2).

Table 1. Oxidative stress index (OSI) in cortex, striatum, hippocampus and thalamus of rats with lesion of central dopaminergic system after propofol administration (group 4) compared with rats with lesion of central dopaminergic system without propofol administration (group 2)

OSI [arbitrary unit]	Cortex	Striatum	Hippocampus	Thalamus
Group 2	4.10 [3.02–5.31]	9,05 [6,42–13.00]	5.25 [4.80–5.73]	9.02 [5.09–13.73]
Group 4	1.24 [1.17–1.60]	3.18 [3.03–4.23]	2.25 [1.99–2.43]	2.62 [2.11–4.00]
P	<0.001	<0,05	<0.001	<0.05

Values are expressed as median (1st–3rd quartile); n = 8/group

Group 2 – Rats with lesion of central dopaminergic system without propofol administration (Parkinson's disease group), Group 4 – Rats with lesion of central dopaminergic system after propofol administration.

Table 2. Oxidative stress index (OSI) in cortex, striatum, hippocampus and thalamus of healthy rats exposure to propofol (group 3) compared with control group without propofol administration (group 1)

OSI [arbitrary unit]	Cortex	Striatum	Hippocampus	Thalamus
Group 1	3.64 [3.32–4.14]	4.74 [3.81–6.53]	4.96 [2.68–5.28]	3.49 [2.53–4.63]
Group 3	3.11 [2.73–3.42]	3.52 [2.49–4.72]	3.64 [2.39–5.31]	7,76 [6.01–14.23]
P	NS	NS	NS	NS

Values are expressed as median (1st–3rd quartile); n = 8/group

Group 1 – healthy rats without propofol administration (control group), Group 3 – healthy rats after propofol administration.

A statistically significant decrease in MDA levels were observed in all analyzed structures of rats brain rats with lesion of central dopaminergic system (PD model) after administration of propofol (group 4) compared with rats with lesion of central dopaminergic system (PD model) (group 2). The relative response of tissues brain to the administration of propofol was as follow: cortex> striatum>hippocampus>thalamus (39%, 28%, 21%, 20%, respectively) (Table 3).

A statistically significant decrease in MDA level was observed only in the cortex (by 39%) in healthy rats group exposed to propofol (group 3) compared with the healthy rats without propofol administration - control group (group 1) (Table 4).

DISCUSSION

Parkinson's disease is an increasingly common disease mainly for older patients. Different drugs used in anaesthesia may interact with anti-parkinsonian medication and there is question about the optimal anaesthetic management of patients with Parkinson's disease. Increasing number of surgical procedures in PD patients, contributed to the search of medications which properties are not limited to anesthetic ones. Some anesthetics have been proposed as a way of protection against the pathological states associated with oxidative stress. [16, 22]. Propofol is known not only due to its anaesthetic properties, but also to the strong antioxidant properties [28, 32, 34, 37]. Highly lipophilic properties of propofol and effective crossing the blood-brain barrier, make it easily affects the different brain structures [28]. Several mechanisms, including the reduction of the cerebral metabolic rate for oxygen, decrease in intracranial pressure and neutralization of the lipophilic and hydrophilic radicals by both directly scavenging ROS and activating endogenous antioxidant enzymes, may explain the beneficial effects of using propofol against oxidative stress on the brain structures [2]. Antioxidant properties of propofol [24], its lipophilicity and the significant ability to cross the blood-brain barrier [28] suggest that propofol may also affect the oxidant-antioxidant system in PD. The pharmacological brain protection caused by propofol provides an optimal intraoperative condition during neurosurgical operations and can also be useful in the treatment of brain disorders related to oxidative stress such as PD [2]. However, influence of propofol on oxidative-antioxidative status in the brain affected by PD has not been fully evaluated. Therefore, we investigated the effect of propofol on oxidative stress in four different parts of the brain and compared the differences in response to propofol between rats with PD and healthy ones.

Table 3. Malondialdehyde (MDA) concentration in cortex, striatum, hippocampus and thalamus of rats with lesion of central dopaminergic system after propofol administration (group 4) compared with rats with lesion of central dopaminergic system without propofol administration (group 2)

MDA [µmol/g protein]	Cortex	Striatum	Hippocampus	Thalamus
Group 2	1.06 [0.93–1.34]	0.96 [0.88–1.09]	1.09 [1.05–1.20]	0.64 [0.59–0.69]
Group 4	0.65 [0.62–0.71]	0.70 [0.65–0.75]	0.86 [0.80–1.08]	0.51 [0.49–0.60]
P	<0.001	<0.001	<0.05	<0.05

Values are expressed as median (1st–3rd quartile); n = 8/group

Group 2 – Rats with lesion of central dopaminergic system without propofol administration (Parkinson's disease group), Group 4 – Rats with lesion of central dopaminergic system after propofol administration

Table 4. Malondialdehyde (MDA) concentration in cortex, striatum, hippocampus and thalamus of healthy rats exposure to propofol (group 3) compared with control group without propofol administration (group 1)

MDA [µmol/g protein]	Cortex	Striatum	Hippocampus	Thalamus
Group 1	1.22 [1.13–1.22]	0,83 [0.77–0.88]	0.99 [0.95–1.04]	0.56 [0.47–0.57]
Group 3	0.74 [0.66–0.82]	0.86 [0.84–0.87]	0.97 [0.77–1.09]	0.59 [0.52–0.64]
P	<0.001	NS	NS	NS

Values are expressed as median (1st–3rd quartile); n = 8/group

Group 1 – healthy rats without propofol administration (control group), Group 3 – healthy rats after propofol administration.

Separate measurements of different antioxidants and ROS components do not reflect the overall balance of oxidant-antioxidant tissues, and these procedures are labor-intensive, require the use of complicated techniques and cost a lot [1, 29]. Therefore, to evaluate the general protective role of propofol against free radicals, we used the OSI. OSI is an important marker of oxidative stress which indicate on imbalance between the production of ROS and their elimination by antioxidant defense mechanisms. This is defined as the ratio of the total oxidant status (TOS) to total antioxidant capacity (TAC) levels [4, 38]. Our finding has demonstrated that the administration of propofol to rats with lesion of central dopaminergic system (PD model) (group 4), compared to rats with lesion of central dopaminergic system (PD model) that did not receive propofol (group 2), resulted in a significant reduction of the OSI levels by 71% in thalamus, 70% in cortex, 65% in striatum and 57% in hippocampus. The antioxidant effect of propofol on all the analyzed brain structures of rats with lesion of central dopaminergic system (PD model) seems to result from its ability to bind to the cell membrane phospholipids and directly react with free radicals, leading to the formation of products with much lower reactivity [21]. Another equally important propofol mechanism is its ability to stimulate the antioxidant defences [12]. The beneficial effect of propofol on both components of oxidation-antioxidant balance makes that the overall level of oxidative stress is reduced, which may be particularly important for treating diseases related to oxidative stress.

Brain tissues are largely composed of phospholipids, which are rich in polyunsaturated fatty acids. Increased lipid peroxidation lead to the structural modification of membrane, such as the reduction of hydrophobic interior of lipid bilayer, membrane potential depolarization and the inhibition of the transport of proteins and activity of the enzymes [3, 30]. One of the biomarkers used to investigate the intensity of this process is the measurement of MDA. An increasing number of evidences indicate that MDA may have practical application as biomarker of neurodegenerative disorders and indicator for monitoring the effects of antioxidants therapy [35, 36].

Previous studies also showed that propofol has a clear antioxidant effect against lipid peroxidation in animal brain tissues in the various models of oxidative stress [19, 32, 37]; but, only our study analyzed separately the different regions of the brain. We have observed significantly decreased MDA levels after the injection of propofol in all regions of the brains of rats with lesion of central dopaminergic system (PD model), as compared to the control group (group 2). The tissues response to the administration of propofol was as follows: cortex>striatum>hippocampus>thalamus (39%, 28%, 21% and 20%, respectively). The frontal cortex, unlike the other brain regions, contains higher concentrations of polyunsaturated fatty acids, which under oxidative stress conditions are rapidly depleted, which leads to the intensified generation of lipid peroxidation products [5, 23]. In tissues characterized by increased intensity of lipid peroxidation, response to administered propofol is also higher [34], which confirms our current research findings. We have also observed the differences in tissue response to administered propofol between healthy rats and rats with rats with lesion of central dopaminergic system (PD model). In healthy rats treated with propofol (group 3), relative to the control group without propofol (group 1), we observed only statistically significant decrease in MDA levels in the cortex (by 40%), while the changes in other brain structures were statistically insignificant. As mentioned above, a significant decreased MDA level in the cortex may be the result of the increased distribution of propofol to this region, which is particularly sensitive to lipid peroxidation. Our previous study showed that the peripheral tissues response to administered propofol is different in rats with lesion of central dopaminergic system (PD model) and in healthy ones [34]. This study also supports that hypothesis when it comes to different brain tissues. The activity of propofol in patients with PD can differ with respect to the population [10]. Tissue response to propofol administration may depends on the initial oxidative-antioxidative status. As we have observed in PD, under conditions of the increased production of free radicals and insufficiency of antioxidant defense, antioxidant mechanisms of propofol become strengthened, thus protecting the tissues from further oxidative damages. In these conditions, it could be major defense mechanism against oxidative stress caused by enhanced level of ROS. Natural defense mechanisms against free radicals in healthy individuals seem to be sufficient and propofol only stimulates this defense.

CONCLUSION

Our study showed that propofol is effective in inhibition of oxidative stress in all evaluated structures of the brain of rats with lesion of central dopaminergic system (PD model). The benefits for the brain from the administration of propofol are observed especially under conditions of increased oxidative stress observed in Parkinson disease rats.

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