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Influence of propofol on oxidative-antioxidative system parameters in peripheral organs of rats with Parkinson disease

Wpływ propofolu na parametry stanu oksydacyjno-antyoksydacyjnego narządów obwodowych w modelu doświadczalnym u szczurów z chorobą Parkinsona.

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Summary

Aim

Propofol (2,6-diisopropylphenol) is a popular anaesthetic agent with antioxidant properties. The aim of the study was to assess the oxidant-antioxidant system parameters of particular organs (liver, kidney, heart, and lungs) in response to propofol administered to rats with Parkinson's disease and to healthy ones.

Material/Methods

The experiment was performed using 32 Wistar rats divided into four groups (8 rats each). The groups were as follows: 1 control, 2 Parkinson's disease, 3 control with propofol, 4 Parkinson's disease with propofol. Propofol was administered at a dose of 60 mg/kg body weight/IP, 60 minutes before decapitation. Animals were sacrificed and livers, kidneys, hearts and lungs were obtained for further biochemical analyses. The concentration of malondialdehyde (MDA), glutathione reductase (GR) activity, glutathione peroxidase (GPx) activity, glutathione S-transferase (GST) activity and catalase (CAT) activity were determined.

Results

In group 4 compared to group 2 there was observed a significant decrease in the MDA level in liver (71%), kidneys (51%) and heart (12%), increased GR activity in lungs (48%) and heart (34%), and increased CAT activity in liver (104%). In group 3 compared to group 1 there was a significant decrease in MDA level in kidneys (67%) and lungs (14%) and increased GR activity in heart (31%), liver (29%) and lungs (21%).

Conclusions

Propofol can prevent or reduce damage caused by reactive oxygen species (ROS) by stimulating activity of antioxidative enzymes and inhibiting lipid peroxidation. Additionally, the response of tissues to administered propofol is different in Parkinson's disease and in healthy individuals.

Keywords:

propofol • organs • Parkinson's disease • oxidative stress

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Abbreviations **CAT** – catalase, **GPx** – glutathione peroxidase, **GR** – glutathione reductase, **GST** glutathione transferase, **MDA** – malondialdehyde, **PD** – Parkinson disease, **ROS** - reactive oxygen species.

INTRODUCTION

Propofol (2,6-diisopropylphenol) is one of the most popular anaesthetic agents, used in induction and maintaining general anaesthesia. In addition to the anaesthetic properties, it has a number of other beneficial effects. Its powerful antioxidant, immunomodulatory, analgesic and neuroprotective properties are particularly noteworthy. Antioxidant properties of propofol are partially explained by its chemical structure resembling a natural antioxidant alpha-tocopherol, in which a phenolic hydroxyl group capable of removing free radicals is important [30]. It has been shown that propofol inhibits lipid peroxidation, and enhances the antioxidative system for cell protection, thereby protecting tissues against oxidative stress [5]. It is important that propofol reduces oxidative damage not only to the brain [21], but also to the liver, heart, kidney and lungs [25]. This antioxidant properties of propofol may be used in treatment of disorders characterised by intensive production of free radicals. Oxidative damage to the cells as a consequence of excessive production of free radicals may be an important factor involved in the initiation as well as in the subsequent progression of neurodegenerative diseases [28]. Increased aerobic metabolism, lower activity of antioxidant enzymes and increased level of polyunsaturated fatty acids in the cell membrane of neurons makes them more susceptible to oxidative damage [13]. It is postulated that oxidative stress may be an important factor in the development of neurodegenerative diseases such as Parkinson's disease (PD). One hypothesis assumes that excessive production of free radicals causes the loss of dopaminergic neurons in the substantia nigra of the midbrain, which leads to reduction of dopamine content in the striatum and in consequence to disclosure of symptoms of PD [10]. Studies indicate that in the course of PD there is observed decreased activity of antioxidant enzymes, as well as the increased value of oxidative stress markers in the brain and peripheral tissues [12,27], which is a sign of the significant role of oxidative stress in pathogenesis of this disease. This is fundamental to the search for substances with antioxidative properties, whose scope of impact includes both the brain structures and peripheral organs. In the exist-

ing literature there are a few studies evaluating the efficacy of propofol as a substance with antioxidative properties in organs other than the brain (in liver, kidney, lungs and heart) [5,25], while there are no data evaluating these properties in above-mentioned organs in Parkinson's disease. Therefore, the present study aimed at determining the extent to which oxidant-antioxidant systems of particular organs (liver, kidney, heart, and lungs) respond to propofol administered to rats with Parkinson's disease and to healthy ones. In addition, the study analysed whether the response of tissue to injected propofol is different in rats with Parkinson's disease and healthy ones.

MATERIALS AND METHODS

Animals

In this study, male Wistar rats weighing 180-200 g were used. During the experiment the animals were housed in standard conditions of moisture (55-60%), temperature (21-22°C) and lighting (12-hour artificial lighting cycle – day/night 12/12). The animals had free access to food and filtered water. The study was performed in compliance with international guidelines for the care and handling of laboratory animals. The study protocol was approved by the Local Ethics Committee of the Medical University of Silesia in Katowice (permit no. 33/2013).

Experiment

Newborn Wistar rats were randomly divided into two groups and were subjected to the following procedure:

Group I – control rats. On the third day of animals' life desmethylimipramine (20 mg/kg body weight in a 1.0 ml/kg body weight volume, intraperitoneally (IP)) was administered. After one hour, 10 µl 0.1% ascorbic acid solution intracerebroventricular (ICV) administration was performed.

Group II – rats with Parkinson's disease. On the third day of animals' life desmethylimipramine (20 mg/kg body weight in a 1.0 ml/kg body weight volume, IP)

was administered. After one hour, 6hydroxydopamine (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.

Animals were housed with their mothers until 4 weeks of age, and then were separated by sex and placed in separate cages for further biochemical experimentation. The actual experiment was performed using 8-week-old rats. Thirty-two male Wistar rats were divided into four groups (8 rats each). The groups were as follows: 1 control, 2 Parkinson's disease, 3 control with propofol, 4 Parkinson's disease with propofol. The first and second group received only normal saline. The third and fourth group received propofol at a dose of 60 mg/kg body weight/IP. After one hour, animals were sacrificed and livers, kidneys, hearts and lungs were obtained and stored at (-80°C) in a deep freezer for further biochemical analyses.

Tissues preparation

Tissues were homogenized on ice in short cycles of a few seconds after cutting the organs into small pieces. For homogenization 0.9% NaCl solution was used. After mechanical homogenization we used a UP50H ultrasonic processor (Hielscher). In the next step the homogenates were centrifuged at 3000 rpm for 10 minutes and supernatants were used for assay of the oxidant-antioxidant parameters.

Biochemical analysis

The concentration of malondialdehyde (MDA) was assayed by the method of Ohkawa [20]. Glutathione reductase (GR) activity was assayed using the modified semi-automatic method described by Richterich [24]. Glutathione peroxidase (GPx) activity was measured by the method of Paglia and Valentine [22]. The glutathione S-transferase (GST) activity was measured according to the Habig method [9]. Catalase (CAT) activity was assessed according to the method of Aebi [2]. Protein levels in the samples were assayed by the method of Lowry [18].

Statistical analysis

All statistical analyses were done with the "STATISTICA 10" program. The normality of the results distribution was verified using the Kolmogorov-Smirnov test. Due to the small size of the groups we used the non-parametric Mann-Whitney U test, and the data were presented as median with the first and fourth quartiles. Results were considered statistically significant if $p < 0.05$. Lack of statistical significance was presented as NS (non-significant).

RESULTS

In the liver of studied rats we observed an increase in CAT activity (104%) and decrease in MDA concentration (71%) in group 4 compared with group 2. In group 3 we observed an increase in GR activity (29%) compared to group 1 (Table 1).

Studying the heart results we observed an increase in GR (34%) and GPX activity (41%) and a decrease in MDA (12%) in group 4 compared with group 2. In group 3 we observed an increase in GR (31%) and decrease in GPX activity (13%) compared to group 1 (Table 2).

In the lungs of studied rats we observed an increase in GR activity (48%) in group 4 compared with group 2. In group 3 we observed an increase in GR activity (21%), too, and a decrease in MDA concentration (14%) compared to group 1 (Table 3).

Studying the kidney results, we observed a decrease in MDA concentration (51%) in group 4 compared to group 2 and in group 3 (67%) compared to group 1. In group 4 we observed a decrease in GST activity (80%) compared to group 2 (Table 4).

Changes in GR and MDA concentration in the liver, heart, lung and kidney of studied rats are shown in figure 1. The catalase activity in the liver, heart, lung and kidney of studied rats is shown in figure 2.

Table 1. Antioxidant enzymes activity and malondialdehyde concentration in liver's homogenates of studied groups of rats (U Manna-Whitneya test).

	Group 2	Group 4	P 2vs4	Group 1	Group 3	P 1vs3
GR (IU/g protein)	23.87 (18.14-26.62)	25.38 (24.17-30.25)	NS	21.05 (19.67-22.72)	26.41 (24.80-28.52)	<0.001
CAT (kIU/g protein)	780.81 (686.38-856.02)	1651.63 (1368.45-1780.83)	<0.001	1011.29 (922.75-1092.41)	1129.46 (874.03-1369.42)	NS
GPX (IU/g protein)	358.24 (270.57-362.36)	314.99 (235.54-407.75)	NS	326.74 (207.30-351.72)	247.26 (221.02-248.86)	NS
GST (IU/g protein)	12.75 (11.22-14.92)	13.88 (11.98-16.41)	NS	13.28 (11.24-14.67)	14.45 (12.75-14.62)	NS
MDA (umol/g protein)	6.54 (6.25-8.11)	1.95 (1.71-2.45)	<0.001	3.16 (2.64-5.25)	3.20 (1.94-5.35)	NS

Table 2. Antioxidant enzymes activity and malondialdehyde concentration in heart's homogenates of studied groups of rats (U Manna-Whitneya test)

	Group 2	Group 4	P 2vs4	Group 1	Group 3	P 1vs3
GR (IU/g protein)	10.73 (9.31-12.98)	14.81 (14.03-15.32)	<0.001	12.52 (11.55-12.99)	16.28 (15.05-16.06)	<0.001
CAT (kIU/ g protein)	67.9 (63.23-72.95)	66.62 (63.46-72.59)	NS	67.81 (64.03-69.69)	61.33 (58.61-68.60)	NS
GPX (IU/g protein)	50.66 (40.86-60.38)	73.07 (58.94-82.93)	<0.05	67.89 (65.85-71.58)	54.73 (44.28-62.84)	<0.05
GST (IU/g protein)	1.49 (1.41-1.74)	1.63 (1.55-1.68)	NS	1.77 (1.60-1.91)	1.60 (1.44-1.76)	NS
MDA (umol/g protein)	5.22 (4.84-5.68)	4.59 (4.38-4.86)	<0.05	5.94 (5.51-6.47)	6.56 (6.04-6.96)	NS

Table 3. Antioxidant enzymes activity and malondialdehyde concentration in lung's homogenates of studied groups of rats (U Manna-Whitneya test)

	Group 2	Group 4	P 2vs4	Group 1	Group 3	P 1vs3
GR (IU/g protein)	13.55 (11.86-17.01)	21.19 (19.30-22.40)	<0.001	18.52 (17.88-18.59)	20.96 (19.25-25.82)	<0.05
CAT (kIU/ g protein)	61.43 (57.37-69.95)	65.59 (58.67-66.81)	NS	62.88 (58.84-67.29)	65.58 (57.39-69.83)	NS
GPX (IU/g protein)	32.41 (21.85-33.69)	33.07 (29.47-37.03)	NS	26.42 (24.98-31.76)	27.49 (23.72-29.72)	NS
GST (IU/g protein)	1.28 (1.05-1.39)	1.36 (1.20-1.38)	NS	1.38 (1.23-1.68)	1.34 (1.24-1.37)	NS
MDA (umol/g protein)	3.73 (3.40-3.85)	3.97 (3.80-4.21)	NS	3.89 (3.49-4.05)	3.52 (2.87-3.67)	<0.05

Table 4. Antioxidant enzymes activity and malondialdehyde concentration in kidney's homogenates of studied groups of rats (U Manna-Whitneya test).

	Group 2	Group 4	P 2vs4	Group 1	Group 3	P 1vs3
GR (IU/g protein)	17.40 (14.70-18.21)	15.22 (13.30-17.02)	NS	17.83 (17.37-20.10)	17.78 (17.49-19.41)	NS
CAT (kIU/ g protein)	419.15 (400.49-485.82)	399.18 (351.18-426.67)	NS	387.39 (330.96-443.03)	401.80 (343.93-458.70)	NS
GPX (IU/g protein)	105.68 (104.56-127.70)	105.44 (103.31-128.19)	NS	99.96 (80.64-108.87)	88.15 (85.49-118.40)	NS
GST (IU/g protein)	0.91 (0.82-1.10)	0.22 (0.19-0.27)	<0.001	0.48 (0.44-0.59)	0.25 (0.10-0.71)	NS
MDA (umol/g protein)	3.50 (3.30-3.55)	1.78 (1.46-2.07)	<0.001	6.64 (5.60-8.06)	1.73 (1.62-2.95)	<0.001

DISCUSSION

Propofol is an anaesthetic drug commonly used to induce sedation and general anaesthesia [16]. Due to a continuously increasing number of surgical procedures in PD patients, there is a need to seek medications whose effect is not limited solely to anaesthetic. It seems that propofol has such properties, as apart from its doubtless anaesthetic effects it seems to additionally

protect the oxidation-antioxidation system [30]. It was shown that propofol can influence tissues through several mechanisms: it inhibits production of reactive oxygen species, can directly remove already existing ROS, it inhibits lipid peroxidation, and induces expression of antioxidative enzymes [16,17]. The pharmacokinetics of propofol are characterized by a high hepatic extraction ratio and rapid distribution into peripheral tissues and may be different in patients with PD in comparison

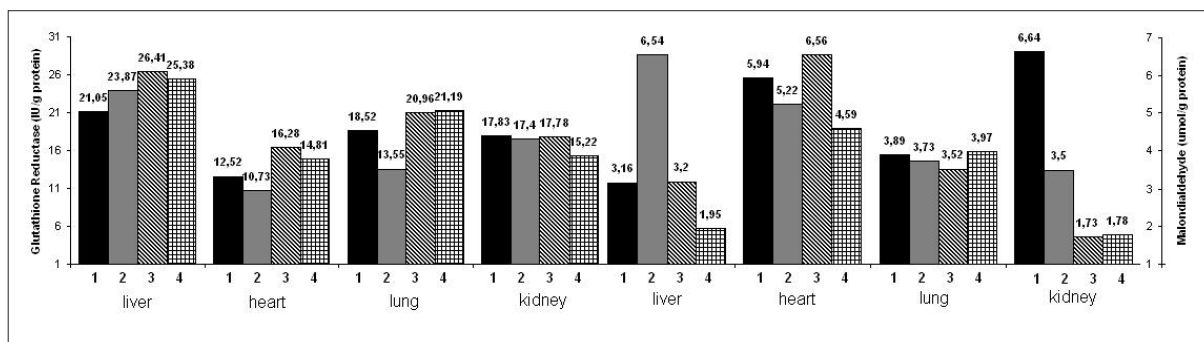


Fig. 1. Glutathione reductase activity and MDA concentration in the liver, heart, lung and kidney homogenates of studied rats; 1 - control, 2 - Parkinson's disease, 3 - control with propofol, 4 - Parkinson's disease with propofol

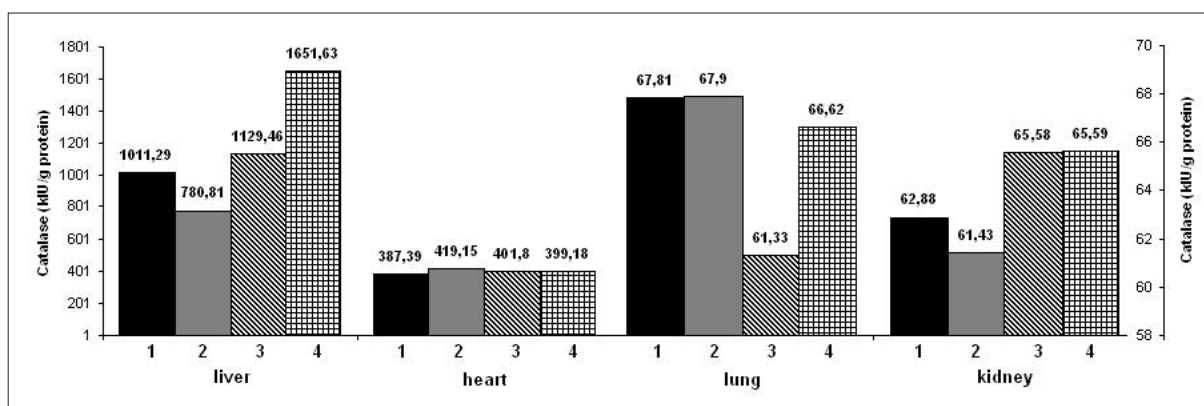


Fig. 2. Catalase activity in the liver, heart, lung and kidney homogenates of studied rats; 1 - control, 2 - Parkinson's disease, 3 - control with propofol, 4 - Parkinson's disease with propofol

to the general population. Therefore, the response to administered propofol may be different in different tissues [7]. Propofol is highly lipophilic, so it easily penetrates all cell membranes, including the blood-brain barrier to the central nervous system [4]. Protective effects of propofol anaesthesia in the brain were documented in various oxidative stress models [6,21]; however, little is known about the possible propofol effect on the oxidant-antioxidant balance in peripheral organs. Currently, no other studies are available concerning the effect of propofol on antioxidative system function and the oxidation stress level in liver, kidneys, heart and lung in an animal PD model.

Evaluation of propofol antioxidative properties has been studied extensively. It was demonstrated that propofol has a positive effect on some parameters of the oxidant-antioxidant system, including inhibition of lipid peroxidation and increase in an activity of antioxidative enzymes in conditions of laboratory-induced intensified oxidative stress [23]. Lipid peroxidation is a cascade of events generating new ROS initiating damage in successive cells. Therefore, by stopping this process not only is already inflicted damage reduced, but also new damage is prevented [19]. To evaluate the degree of lipid peroxidation intensity, process marker levels are determined. MDA, an end product of polyunsaturated

fatty acid oxidation in cell membranes, is a commonly used marker [14]. Our own studies showed that propofol administration to PD rats resulted in reduction of MDA levels by 71% in liver, 51% in kidney, 12% in heart and 6.5% in lungs ($p > 0.05$) compared to PD without propofol. Such significant differences in individual tissues may depend on blood flow in an organ or on its lipid content, that is, on tissue capability to capture propofol. Similar observations were made by Runzer et al., who evaluated the role of propofol in inhibition of lipid peroxidation in conditions of intensified oxidative stress. Results obtained in that study are consistent with ours, as propofol protected organs to a different extent, and the tissue response to propofol administration was as follows: liver>kidneys>heart>lungs [25]. Although the percentage ratio of changes in individual organs differed from that in our study, the tendency of a tissue response to the administered drug remained unchanged. On the other hand, studies of De La Cruz et al. showed that propofol protects against lipid peroxidation mainly in the heart and lungs, and in the kidneys and liver to a lesser extent [5]. In the above models, the propofol administration route and the administered dose were different, and this may explain the differences in obtained results. Furthermore, the experimental method can affect quantitative capture of the drug in individual tissues. Our studies also show that the tis-

sue response to administered propofol in healthy individuals is different to that in PD individuals. In healthy individuals treated with propofol, the largest percentage drop in the MDA level was observed in kidneys (67%) and lungs (14%) compared to healthy individuals without propofol, while changes in heart and liver were statistically insignificant (8% and 6.4%, respectively). Such large differences in tissue response to propofol in individuals with PD and in healthy ones can result from increased production of free radicals in PD [8], and ROS can easily damage lipid membrane structures in various organs [15,27, 26]. In these conditions, propofol inhibits lipid peroxidation processes, and this was reflected in reduced MDA levels in individual organs in PD individuals. On the other hand, in healthy individuals natural antioxidative mechanisms seem to be sufficient to fight free radicals, and propofol only enhances this fight. A higher MDA level is only found in the kidney, as an organ excreting this compound from the body, so the natural concentration of MDA in the kidney is higher, and here propofol-induced reduction in its level is significant. Furthermore, changes observed in the kidney may also result from a naturally higher susceptibility of this organ to lipid peroxidation; therefore, its response to administered propofol would also be higher.

The studies report that propofol, apart from its doubtless ability to directly sweep free radicals, can also increase organ ability to defend against ROS by stimulating the antioxidative system function, thus stimulating the body to fight ROS [1,23]. Our studies show that propofol increases activity of antioxidative enzymes in all studied organs, excluding kidneys. Similar observations were made by Adaramoye et al. [1] Therefore, in the kidney the only mechanism stimulated by propofol is lipid peroxidation inhibition, and this can additionally explain such a significant reduction in the MDA levels both in PD and in healthy individuals. It was shown that propofol administration to PD individuals results in a GR activity increase, mainly in the lungs (by 48%) and the heart (by 34%), compared to PD individuals without propofol, while in the liver an increase in CAT activity by 104% was observed. In healthy individuals with propofol, an increase in GR activity was observed in heart, liver and lungs (increase by 31%, 29% and 21%, respectively) compared to healthy controls. Our studies show that

the antioxidative mechanism stimulated by propofol depends on the cell type, as each cell has its own mechanism for defence against ROS [3], and different mechanisms can be stimulated in different disorders. However, mechanisms responsible for antioxidative defence stimulation by propofol remain unexplained. The overall effect of propofol in the organs may be a combination of its effects on various cells [29]. Studies conducted by De La Cruz et al. [5] and Ranjbar et al. [23] also confirm that propofol increases activity of GSH-dependant enzymes in different organs. In our studies, a significant increase was observed in activity of GR, a very important enzyme maintaining a correct reduced/oxidised glutathione ratio. It is thought that a low level of reduced glutathione and GSH-dependant enzyme dysfunction can contribute to progression of neurodegenerative disorders, including PD [11]. Therefore, propofol, by stimulating GR activity, increases the available pool of reduced glutathione, thus protecting tissues against a deteriorating ROS effect and contributing to inhibition of further disease progression.

Our studies show that propofol can prevent or reduce damage caused by reactive oxygen species by stimulating activity of antioxidative enzymes and inhibiting lipid peroxidation in peripheral organs in healthy and in PD individuals. Additionally, these properties can be used during procedures in PD patients with propofol-induced anaesthesia, as an additional protection against ROS in peripheral organs.

In conclusion, our studies supplement previous knowledge on antioxidative properties of propofol. A beneficial effect of propofol on the oxidant-antioxidant balance in peripheral organs was confirmed. Additionally, our studies show that the tissue response to administered propofol is different in PD and in healthy individuals. Furthermore, propofol can stimulate various antioxidative defence mechanisms, but the way in which these mechanisms are activated remains unexplained. Future experimental studies should focus on explaining the way in which propofol influences the antioxidative system. It is also necessary to conduct further studies evaluating the effect of propofol on oxidant-antioxidant system parameters in long-term observations.

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