Volume 5-1, 2023, DOI: 10.59124/guhes.1223446

GUHES

Journal of Gazi University Health Sciences Institute

journal homepage: https://dergipark.org.tr/tr/pub/guhes

Desfluran Protects The Brain Against The Oxidant Activity of Acute Hyperglycemia in Diabetic Rats, Comparison with Sevoflurane

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Article info:

Received: 26.12.2022

Accepted:14.01.2023

Keywords:

Diabetes Mellitus,
sevoflurane,
desflurane,
brain,
antioxidant system

Abstract

In this study, we investigated the effects of sevoflurane and desflurane administration on the oxidant and antioxidant system in the brain of acute hyperglycemia in diabetic rats. In the study, 30 male Wistar Albino rats were randomly divided into five groups. Diabetes was induced by administering a single dose of intraperitoneal streptozotocin (55 mg/kg) to rats except for the control group (C). To create acute hyperglycemia in diabetic groups, which were hyperglycemia (DH), desflurane (D), and sevoflurane (S) groups, 2.5 g/kg glucose was administered intraperitoneally. After glucose administration, desflurane 6% and sevoflurane 2.3% mixed with 4 L/min oxygen were administered for 2 hours, by which minimal alveolar concentration for rats would be one. Afterward, the animals were sacrificed, and their brain tissues were prepared for biochemical analysis. Catalase (CAT), glutathione-s-transferase (GST), paraoxonase (PON) activities, and TBARS levels were measured to determine oxidant and antioxidant status. GST activity was significantly lower in group D than in group DH ($p=0.001$). The PON activity was significantly lower in the D group compared with other groups ($p<0.001$). In the S group, PON activity was significantly lower than in the diabetic control (DC) group and DH groups ($p=0.022$, $p=0.020$, respectively). TBARS level was significantly lower in group D than in group DH ($p=0.013$). As a result, desflurane decreases GST and PON activity and TBARS levels more than sevoflurane. In terms of lipid peroxidation, desflurane shows more protective properties than sevoflurane. Since our study is the first study in this field, it should be supported by other studies to be carried out.

1. Introduction

Diabetes is a prevalent chronic metabolic disorder characterized by hyperglycemia that significantly impacts health and quality of life, affecting more than estimated to be 536,6 million people globally in 2021 (Sun et al., 2022). The prevalence of diagnosed diabetes is progressively increasing due to population growth, aging, unhealthy diet, and obesity. Thus, the number of diabetic patients undergoing surgery is increasing day by day. Such acute diseases, infections, stress, and surgery in people with diabetes may increase blood glucose levels. The activation of the sympathetic nervous system characterizes the stress response to surgery. The activation of the sympathetic system increases the secretion of hormones such as cortisol and catecholamines and decreases the release of the insulin hormone (Shilling & Raphael, 2008).

The patient's blood glucose level increases, and several biochemical reactions occur in the body due to the decrease of the blood insulin level. All of these reasons are a response to occur acute hyperglycemia (Turina, Fry, & Polk Jr, 2005).

Increased oxidative stress and reactive oxygen species (ROS) cause unwanted clinical outcomes in diabetes. The main factor in the formation of ROS is the autoxidation of cells that contain glucose and non-enzymatical glycosylation. In addition, see some changes in the antioxidant system and weakened cellular scavenging activity against oxidative stress in diabetes mellitus (Wei et al., 2009). Acute hyperglycemia induces free radicals, and thus this situation leads to oxidative damage of biomolecules such as DNA, proteins, lipids, and carbohydrates (Choi, Benzie, Ma, Strain, & Hannigan, 2008). Control of the oxidants and antioxidant system has a significant role in the prevention of this occurred complications, and this control provided to any endogenous and exogenous antioxidant systems (Irshad & Chaudhuri, 2002).

Sevoflurane (released in 1988) and desflurane (released in 1992) are anesthetic agents used in surgery (Butterworth Iv, Mackey, & Wasnick, 2022). There is some research to prove the effects of sevoflurane and desflurane on oxidants- the antioxidant system and decrease the TBARS level (Liang et al., 2021; Molin et al., 2014; Türkan et al., 2011).

We investigate the effects of sevoflurane and desflurane on the brain oxidant-antioxidant system in diabetic rats during the acute hyperglycemia period first time in literature.

Materials and Methods

The Animal Care and Utilization Committee approved the study protocol of the Gazi University Faculty of Medicine, Ankara, Türkiye.

2.1. Animals

The study included 30 male Wistar rats (225 g to 300 g body weight) obtained from the GUDAM Animal Research Facility. The rats were housed in cages under standard hygienic conditions, with light and dark cycles exchanging every 12 h. They received standard rat feed and had free access to water up to 2 hours before anesthetic administration.

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2.2. Experimental Design

Thirty male Wistar rats were divided randomly into five groups: Control (group C, n=6), diabetic control (group DC, n=6), diabetic-hyperglycemic (group DH, n=6), desflurane (group D, n=6), and sevoflurane (group S, n=6).

Diabetes induced by a single intraperitoneal injection of streptozotocin at a dose of 55 mg/kg to DC, DH, D, and S groups. Rats whose blood glucose levels exceeded 250 mg/dl after 72 hours of streptozotocin injection were classified as diabetic. We injected 2.5 g/kg glucose intraperitoneally into Group DH. In addition, 2.5 g/kg glucose was injected intraperitoneally to induce hyperglycemia before the administration of anesthetic to groups D, and S. After glucose injection into groups D and S, each group of animals was placed separately in a ventilated inhalation chamber. After the cap was closed, group S rats were exposed to 2% sevoflurane, and group D rats to 6% desflurane evaporated at 4L/min continuous oxygen flow. Anesthesia continued for two hours, during which time we monitored animal movements and breathing. At the end of the anesthesia, the rats were sacrificed, and their brain tissues were removed. Tissue samples were stored at -80 °C until the day of analysis.

2.3. Biochemical analysis of oxidant/ antioxidant parameters

Tissue samples were homogenized in a cold saline solution at 4000 rpm (Heidolph Instruments GMBH&CO KGDiax 900 Germany®), and homogenates centrifuged at 5000 g in the refrigerated centrifuge (Hermle Labortechnik GMBH Z 323 K Germany®) for 20 min., and supernatants collected. The supernatants were used to analyze CAT, GST, and PON activity and measured TBARS level, as described below. We used thiobarbituric acid (TBA) to measure TBARS levels to detect and quantify lipid peroxidation in supernatants, which method was described by Van Ye (Van Ye et al., 1993). 1,1,3,3-tetraethoxy propane used as standard. This method is based on forming the red adduct in the acidic medium between thiobarbituric acid and MDA. Thiobarbituric acid reactive substances were measured at 532 nm. Reasons recorded as nmol/mg.protein.

After 10.000 g/min centrifuged for 60 minutes, collected the supernatants then analyzed for detecting CAT, PON and GST enzyme activities. Those analyzes use the method described by Aebi (Aebi, 1984) and Habig (Habig, Pabst, & Jakoby, 1974).

2. Results

Times CAT activity statically significantly decreased in brain tissue's desflurane and sevoflurane groups compared to controls ($p=0.007$, $p=0.015$ respectively) (Table 1, Figure 1).

Statistical significance for GST activity was seen only between the hyperglycemia and desflurane groups. Brain GST activity was significantly lower in the desflurane group than in the hyperglycemia group ($p=0.001$) (Table 1, Figure 2).

Compared to controls, PON activity statically significantly lowered in the desflurane group in brain tissue ($p<0.001$) (Table 1). In addition, in the desflurane group, when compared to diabetes-control, hyperglycemia and sevoflurane group values significantly decreased ($p<0.001$) (Table 1).

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Table 1: Rat brain tissue oxidative status parameters [Mean ± SEM]

GROUPS	CAT (IU/mg pr)	GST (IU/mg pr)	PON (IU/mg pr)	TBARS (nmol/mg pr)
Control (C)	405,3 ± 28,9	4,58 ± 0,92	324,4 ± 88,0	12,4 ± 4,88
Diabetes-Control (DC)	269,8 ± 44,4	4,42 ± 0,99	402,1 ± 88,6	12,7 ± 4,4
Hyperglycemia (DH)	312,1 ± 45,1	4,7 ± 0,49	377,7 ± 70,3	13,5 ± 2,73
Desflurane (D)	184,6 ± 37,9	3,52 ± 0,16	160,3 ± 21,1	8,82 ± 1,84
Sevoflurane (S)	213,0 ± 39,5	4,04 ± 1,19	267,4 ± 47,4	9,9 ± 3,7

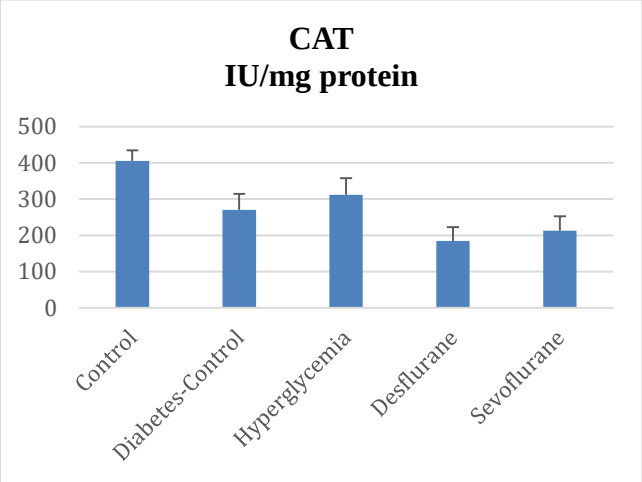

Figure 1. Brain tissue CAT Activity. Data are represented as the mean ± SEM. Differences are considered statistically significant at: *p < 0.05, **p < 0.001, compared with the hyperglycemia

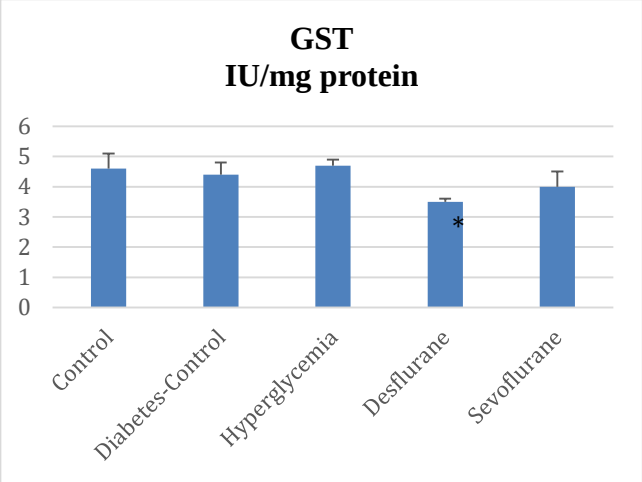

Figure 2. Brain tissue GST Activity. Data are represented as the mean ± SEM. Differences are considered statistically significant at: *p < 0.05, **p < 0.001, compared with the hyperglycemia.

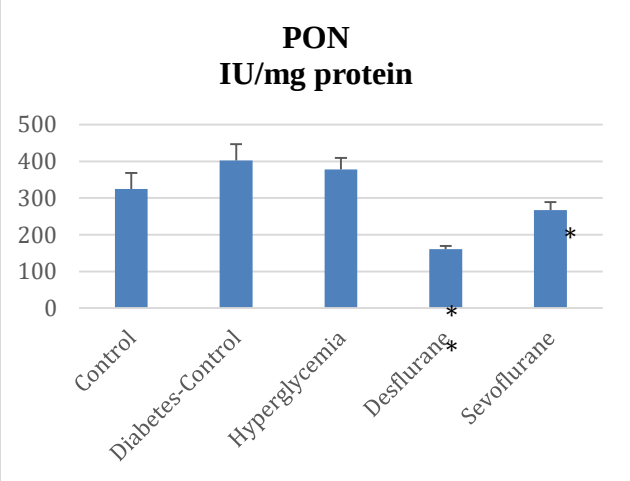

Figure 3. Brain tissue PON Activity. Data are represented as the mean ± SEM. Differences are considered statistically significant at: *p < 0.05, **p < 0.001, compared with the hyperglycemia.

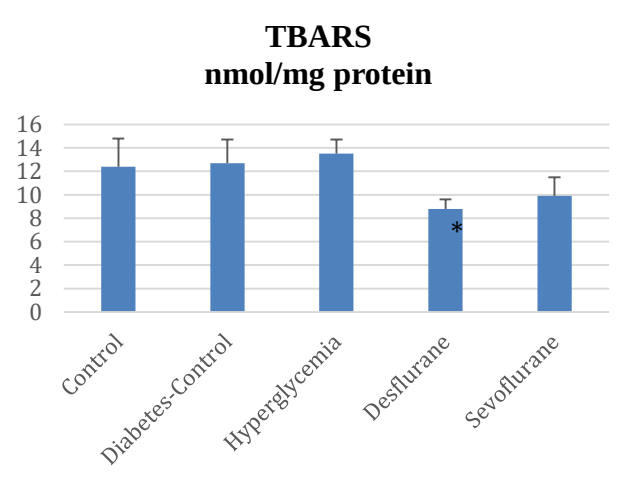

Figure 4. Brain tissue PON Activity. Data are represented as the mean ± SEM. Differences are considered statistically significant at: *p < 0.05, **p < 0.001, compared with the hyperglycemia

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Sevoflurane group values are significantly lower than diabetes-control and hyperglycemia values (p=0.022, p=0.020, respectively) (Table 1, Figure 3).

The amount of TBARS, a lipid peroxidation marker, is statistically only seen between the hyperglycemia and desflurane groups. Desflurane groups' TBARS levels were significantly lower than the hyperglycemia groups' TBARS levels (p=0.013) (Table 1, Figure 4).

When comparing the sevoflurane and desflurane groups, only a difference was observed in terms of PON enzyme activity (p<0,05) (Table 1, Figure 3).

3. Discussion

The number of diabetics is increasing daily; therefore, the number of people with diabetes undergoing surgery is also increasing. Acute hyperglycemia occurs in diabetic patients when they are under stress (Galindo, Fayfman, & Umpierrez, 2018). Nowadays, research about sevoflurane and desflurane, forming oxidative stress and protection role against free radicals' harmful effects, are increasing daily. Our investigation results will help future research. There are many defense mechanisms to eliminate the free radicals formed by metabolic reactions and decrease the harmful effects of free radicals. Some of these free radicals quenching enzymes as a member of this defense mechanism are catalase (CAT), superoxide dismutase (SOD), and glutathione-s-transferase (GST) (Santos-Sánchez, Salas-Coronado, Villanueva-Cañongo, & Hernández-Carlos, 2019). Oxidative stress is an imbalance between the antioxidant system and free radicals, which causes peroxidation of the lipid layer in the cell (Yaribeygi, Sathyapalan, Atkin, & Sahebkar, 2020).

Research on humans and several animal species reported the effects of sevoflurane and desflurane on the oxidant-antioxidant system (Erbas et al., 2015; Wong et al., 2006; Yue et al., 2015).

TBARS level measurement was used in the assessment of lipid peroxidation. Studies on humans (Koksal, Sayilgan, Aydin, Uzun, & Oz, 2004; Türkan et al., 2011) and animals (Akin et al., 2015; Koksal et al., 2004; Sato, Fujii, & Yuge, 1994) that used sevoflurane and desflurane show varied results about TBARS levels. Koksal et al. (Koksal et al., 2004) studied the effects of sevoflurane and desflurane on lipid peroxidation during laparoscopic cholecystectomy. Due to their result, the MDA level of the desflurane group is higher than the sevoflurane group. As a result of their study, desflurane may be more harmful than sevoflurane cause of the systemic and regional lipid peroxidation effects of desflurane.

Sato et al. (Sato et al., 1994) researched the in vivo and in vitro effects of sevoflurane-induced lipid peroxidation in the guinea-pig liver. They exposed the animals to air, 0.5% halothane, and 1.2% sevoflurane. The extent of lipid peroxidation was measured by the level of thiobarbituric acid reactive products 12 hr after exposure. As a result of this study, sevoflurane significantly increased thiobarbituric acid-reactive products, and sevoflurane potentially caused lipid peroxidation.

Turkan et al. (Türkan et al., 2011) studied to evaluate liver, brain, kidney, and lung tissue oxidative stress in rats exposed to desflurane and sevoflurane.

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They administrated sevoflurane (8 %) to the sevoflurane group and desflurane (4 %) to the desflurane group. After four hours of exposure to sevoflurane and desflurane, they measured the levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). Exposure to anesthetics decreased brain MDA levels compared to control. Our study results show similarity to Turkan's research results. In our study, TBARS level significantly decreased in the desflurane group compared to the hyperglycemia group.

Akın et al. (Akin et al., 2015) aimed to investigate the effects of various anesthetics on MDA levels, glutathione peroxidase activity, and antioxidant capacity. They observed that in Group S, levels of MDA decreased.

Dikmen et al. (Dikmen et al., 2007) determined that the CAT, SOD, GST, GSH-Px, and MDA levels were higher in the sevoflurane group than in the desflurane group. Our research shows similar results to Dikmen and Akın's investigation. CAT, GST, and TBARS levels were higher in the sevoflurane group than in the desflurane group, but these results were statistically nonsignificant. Desflurane group, the TBARS level is significantly lower than hyperglycemia, compatible with the literature. According to these results, increased lipid peroxidation in the brain in the acute hyperglycemia period, sevoflurane, and desflurane decreased the antioxidant enzyme activity. However, only desflurane's effect is statistically significant.

Catalase is the enzyme responsible for decomposing hydrogen peroxide into water and oxygen (Claiborne, 2018).

In the study of volatile anesthetics effects on CAT levels, Dikmen et al. (Dikmen et al., 2007) determined an increase in CAT enzyme activity; on the contrary, Watanabe et al. (Watanabe, Kamagata, Tsuboko, & Sakamoto, 2012) determined a decrease in the level of CAT activity. Compared to the control group, the desflurane and sevoflurane groups' enzyme activity was significantly lower for our reasons which parallels Watanabe's result.

GST enzymes' role is the detoxification of metabolites which environmental origin and anesthetics. Research about sevoflurane and desflurane effects on GST; Dikmen et al. (Dikmen et al., 2007) found high, Watanabe et al. (Watanabe et al., 2012) found low, and our findings are significantly lower in the desflurane group than hyperglycemia group.

Paraoxonase enzyme (PON) is an antioxidant enzyme composed of three members (PON1, PON2, and PON3). PON1 is expressed in the liver, PON2 is expressed in the brain, liver, kidney, and testis, and PON3 is expressed in the kidneys. Due to the hyperglycemia predisposition to oxidative stress emerged paraoxonase role in diabetes (Yehuda et al., 2016).

Nair et al. (Nair, Shah, Taggarsi, & Nayak, 2011) studied 370 patients with type 2 DM, PON-1 activity lower than the control group. However, in patients with type 1 DM, PON-1 activity did not change compared to the control group.

Parmaksiz et al. (Parmaksız, Atak, Yavuz, & Şirikçi, 2011) researched the effects of aminoguanidine on serum paraoxonase activity in diabetic rats.

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They found the serum PON activity lower in the diabetic group than in the control group. Only the desflurane groups' enzyme activity significantly decreased compared to the control group, but when compared to the diabetes-control and hyperglycemia groups, either anesthetic showed a significant decrease

4. Conclusion

Results show that desflurane administration decreased the activity of antioxidant enzymes compared to sevoflurane administration. Likewise, lipid peroxidation levels decreased after sevoflurane and desflurane administration. Our research has to be supported by other experimental studies because our investigation is the first research on this subject.

5. Statistical analysis

For statistical analysis, we used SPSS statistics software (version 26.0). Data expressed as mean ± standart error. The differences between the groups were compared using the Kruskal-Wallis variance analysis and Student's t-test. A P value of less than 0.05 was considered statistically significant.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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