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Two fighters against oxidative stress in peripheral organs in Parkinson's Disease: Brain-derived neurotrophic factor and hydrogen sulfide

Parkinson Hastalığında periferik organlardaki oksidatif strese karşı iki savaşçı: Beyin kaynaklı nörotrofik faktör ve hidrojen sülfit

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ABSTRACT

Aim: Parkinson's disease, which is a neurodegenerative disorder, has adverse consequences on peripheral organs as well as the brain. This study aims to investigate the effects of brain-derived neurotrophic factor and hydrogen sulfide on liver, kidney, stomach and intestine in Parkinson's disease model created in mice.

Materials and Methods: To assess the achievement of the Parkinson's disease model and the effects of brain-derived neurotrophic factor and hydrogen sulfide on this model, animals in all groups were subjected to motor behavior tests. Oxidative stress in peripheral organs was determined biochemically by measuring total oxidant and total antioxidant levels. It was also evaluated histologically in terms of tissue damage and cellular degeneration.

Results: According to the motor behavior tests it was revealed that hydrogen sulfide increased motor performance and coordination against Parkinson's disease and decreased bradykinesia. Experimental Parkinson's Disease and inhibition of the brain-derived neurotrophic factor caused cellular changes in the liver, kidney, and intestine indicating oxidative stress-induced degeneration. It was revealed that hydrogen sulfide protects the histological structure especially in the liver and intestinal tissue and supports the process by increasing the antioxidant capacity in the liver and decreasing the oxidant capacity in the intestine.

Conclusion: Brain-derived neurotrophic factor and hydrogen sulfide have different but generally protective effects on oxidative stress in peripheral organs due to Parkinson's disease.

Keywords: Brain derived neurotrophic factor, hydrogen sulfide, oxidative stress, Parkinson's disease, peripheral organs.

ÖZ

Amaç: *Nörodejeneratif bir hastalık olan Parkinson hastalığının beyinde olduğu gibi periferik organlarda da olumsuz sonuçları vardır. Bu çalışmada farelerde oluşturulan Parkinson hastalığı modelinde beyin kaynaklı nörotrofik faktör ve hidrojen sülfitin karaciğer, böbrek, mide ve bağırsak üzerindeki etkilerinin araştırılması amaçlanmaktadır.*

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Gereç ve Yöntem: *Parkinson hastalığı modelinin başarısını ve beyin kaynaklı nörotrofik faktör ile hidrojen sülfitin bu model üzerindeki etkilerini değerlendirmek için tüm gruplardaki hayvanlar motor davranış testlerine tabi tutuldu. Periferik organlardaki oksidatif stres, biyokimyasal olarak toplam oksidan ve toplam antioksidan seviyeleri ölçülerek belirlendi. Ayrıca histolojik olarak doku hasarı ve hücresel dejenerasyon bakımından değerlendirildi.*

Bulgular: *Motor davranış testlerine göre hidrojen sülfitin Parkinson hastalığına karşı motor performansı ve koordinasyonu arttırdığı, bradikineziyi azalttığı ortaya çıktı. Deneysel Parkinson hastalığı ve beyin kaynaklı nörotrofik faktörün inhibisyonu, karaciğer, böbrek ve bağırsakta oksidatif stresin neden olduğu dejenerasyona işaret eden hücresel değişikliklere neden oldu. Hidrojen sülfitin özellikle karaciğer ve bağırsak dokusunda histolojik yapıyı koruduğu ve karaciğerde antioksidan kapasiteyi artırarak, bağırsakta ise oksidan kapasiteyi azaltarak süreci desteklediği ortaya çıktı.*

Sonuç: *Beyin kaynaklı nörotrofik faktör ve hidrojen sülfitin, Parkinson hastalığına bağlı olarak periferik organlarda meydana gelen oksidatif stres üzerinde, farklı ancak genel olarak koruyucu etkileri vardır.*

Anahtar Sözcükler: *Beyin kaynaklı nörotrofik faktör, hidrojen sülfit, oksidatif stres, Parkinson hastalığı, periferik organlar.*

INTRODUCTION

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder that generally affects older adults. It results from the pathophysiological loss of dopaminergic neurons in the substantia nigra (SN) and the formation of neuronal Lewy bodies (1). Although genetic and environmental influences leading to mitochondrial dysfunction, oxidative stress, neuroinflammation and changes in neurotransmitter receptors appear to be possible triggers in PD, information on the onset of the disease is still limited (2, 3).

Oxidative stress, mitochondrial dysfunction, or reactive oxygen species (ROS) play a role in neuronal death. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) destroys dopaminergic neurons in the SN by causing oxidative stress and is extensively used to create establish animal models of PD (4). Increasing evidence shows that PD does not only affect the central nervous system (CNS), but is also a systemic disease that affects peripheral organs too (5-7). Although medical pharmacological treatments and surgical interventions are being made, definitive treatments to modify PD are still lacking.

Brain-derived neurotrophic factor (BDNF), member of the neurotrophins, supports the function of the CNS. By binding to its receptor, tyrosine kinase receptor-B (TrkB), BDNF affects majority of physiological cell functions. The important role of the BDNF-TrkB pathway in the disruption of motor and cognitive abilities in PD has been demonstrated by experiments on animal models in which BDNF levels are reduced due to genetic modification (8). Despite the fact that BDNF and TrkB proteins are found in many tissues, including the CNS as well as liver (9), kidney (10), pancreas (9), gastrointestinal organs (11-13), skeletal muscle (9) and adipose tissue (9), their metabolic functions in peripheral organs are still not fully understood.

Hydrogen sulfide (H_2S) is a gaseous signal molecule produced endogenously from L-cysteine in various tissues (14), it exerts vasodilator, antioxidant, antiapoptotic and anti-inflammatory effects in the brain and peripheral organs and is a signaling molecule, neuromodulator and cytoprotectant (15-17). In studies, it has been observed that H_2S donors are protective and provide therapeutic benefit in animals with experimental PD models (18, 19).

Although PD mainly affects the CNS, studies show that deterioration also occurs in peripheral organs in this process. Protection of peripheral organs may be effective in both slowing down the course of the disease and reducing the symptoms experienced.

MATERIALS and METHODS

Experimental Design

Experimental procedures in animals were performed in accordance with the Laboratory Animal Care and Use Guidelines and were approved by the Experimental Animals Local Ethics Committee, Giresun University (approval date: 16/12/2022, number: 2022/1). Forty-two adult C57BL/6 male mice (four-five months old, 25-30 g) were evenly and randomly divided into six groups as control, K252a, PD, PD+K252a, PD+NaHS and PD+NaHS+K252a, after seven days of adaptation period in the experimental environment (21±2ºC constant temperature and 40-60% humidity, 12-hour day/night cycle, feeding in separate cages).

Drug Administration

Mice in the control group were injected with distilled water for the duration of the experiment (30 days). K252a (50 µg/kg) (BioVision, Waltham, USA), a TrkB receptor antagonist, was given to the K252a group for 14 days, starting from the 16th day of the experimental program (20). In the PD group, an experimental PD model was created as a result of consecutive injections of MPTP (4x20 mg/kg) administered at two-hour intervals on the 23rd day (20). K252a was applied to the PD+K252a group for 14 days, starting from the 16th day of the experimental program, and an experimental PD model was created by applying MPTP every 2 hours on the 23rd day. Sodium hydrosulphite (NaHS, 5.6 mg/kg/day) (Merck, Istanbul, Turkey) was given to the PD+NaHS group as a H_2S donor for 30 days (21), and an experimental PD model was created on the 23rd day with consecutive MPTP injections. Finally, NaHS injection was applied to the PD+NaHS+K252a group throughout the experimental period, K252a injection was applied from the 16th day for 14 days, and MPTP injections were administered on the 23rd day. All injections were performed intraperitoneally.

Motor Behavior Tests

To assess the achievement of the PD model and the effects of BDNF and H_2S on this model, animals in all groups were subjected to motor behavior tests on day 30 of the experimental program. The tests were repeated three times for all mice in the groups and the results obtained were arithmetically averaged. Balance beam test was applied to evaluate the motor performance and coordination. Time taken for the subjects to move 55 cm on a six mm diameter rod at a height of 10 cm from the ground was recorded. Mice were accustomed to the rod with three trials at five-minute intervals prior to the test (20). To reflect bradykinesia in the PD model the pole test was applied. A wooden pole with a rough surface of 1.5 cm diameter and 55 cm in height was placed vertically at the bottom of the cage. The time of turning upside down and descending to the cage floor of the mice placed on the pole with their heads up were recorded. Mice were accustomed to the pole with three trials at 30 second intervals prior to the test (20).

Tissue Removal

At the end of the experimental period, mice in all groups were sacrificed under anesthesia with ketamine (80 mg/kg, i.p.) and xylazine (16 mg/kg, i.p.) diluted in saline. Half of the excised liver, kidney, stomach and intestinal tissues were taken into 10% neutral formalin for histological examinations, while the other half was frozen at -80ºC for biochemical analyses.

Histological Analyses

Tissues were embedded in paraffin after routine histological procedures, and then five µm thick sections were taken. The sections were examined under a light microscope after staining with Hematoxylin-Eosin (H-E) and scored between 1-3, in terms of tissue damage and cellular degeneration (depending on the presence of hypertrophic or shrunken cells, whether the cell borders are clear or not, and whether there is increased eosinophilia, cytoplasmic vacuolization and pyknotic nuclei in the cells, 1: low, 2: moderate, 3: severe).

Biochemical Analyses

Tissues were homogenized and total antioxidant and total oxidant status (TAS and TOS) were measured with commercially available kits (Rel Assay, Düsseldorf, Germany). Results are given as mmol Trolox equivalents/L for TAS, and as micromolar hydrogen peroxide equivalents per liter (µmol H_2O_2 equivalents/L) for TOS.

Statistical Analyses

GraphPad Prism 9.0 program was used for statistical analysis. All obtained data was demonstrated as “mean±standard deviation”. Tukey post hoc test was applied following one-way analysis of variance (ANOVA). 'P' values less than 0.05 were considered statistically significant.

RESULTS

Motor Behavior Tests Results

Mice in the PD (36.88±12.57 sec) and PD+K252a (39.09±18.52 sec) groups had longer time to cross the distance in the balance beam test than the control group (8.25±1.00 sec). This time decreased in the PD+NaHS (14.52±4.49 sec) and PD+NaHS+K252a (16,81±6,00 sn) groups, approaching the values of the control group. There was no statistically significant difference between the PD+NaHS and PD+NaHS+K252a groups (Figure-1A). Mice treated with MPTP exhibited a longer time to turn upside down (25.48±7.79 sec) and to descend (14.54±7.20 sec), than the control group (4.47±1.50 sec turn upside-down and 4.62±0.93 sec ground descent) in the pole test (Figure-1B and 1C). The time to turn upside down in the PD+NaHS group (10.88±2.88 sec) was diminished by NaHS treatment when compared to the PD group. No such improvement in head-downturn time was observed in the PD+NaHS+K252a group (25.71±12.98 sec) (Figure-1B). Although there was a decrease regarding the time to descend to the ground in the the PD+NaHS group (11.57±2.07 sec), it was not statistically different from the PD group. The value was similar in the PD+NaHS+K252a group (13.38±2.16 sec) (Figure-1C).

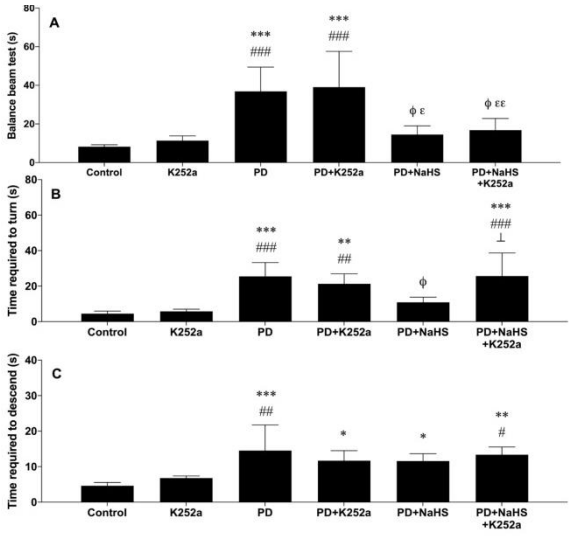

Figure-1. Balance beam test **(A)** and pole test **(B** and **C)** results applied to control and experimental groups (difference from control *p<0.01, **p<0.001, ***p<0.0001, K252a #p<0.05, ##p<0.01, ###p<0.001, PD ϕp<0.01, PD+K252a εp<0.01, εεp<0.01, PD+NaHS ⊥p<0.01).

Histological Analyses Results

The liver tissue's histological structure in the K252a group (0.42±0.53) was found to be similar to the control group (0.28±0.48). It was noticed that the typical polygonal shapes of the hepatocytes were distorted, they became hypertrophic, and the cell borders were less clear and the sinusoids narrowed in the PD (1.71±0.48) and PD+K252a (2.00±0.57) groups, compared to the control group. Additionally, increased eosinophilia was observed in these groups. The histological structure in the PD+NaHS group (1.00±0.57) was closer to the control group. In the PD+NaHS+K252a group (1.57±0.53), the histological structure was found to be similar to the PD and PD+K252a groups (Figure-2A-F and Figure-6A). The histological structure of kidney sections of K252a (0.71±0.48), PD (0.85±0.69) and PD+NaHS (0.57±0.53) groups were similar to the control group (0.42±0.53). It was noticed that some tubular cells became hypertrophic and cell borders were less clear and tubule lumens narrowed in PD+K252a (1.42±0.53) and PD+NaHS+K252a (1.85±0.69) groups (Figure-3A-F and Figure-6B). Additionally, slightly increased eosinophilia was observed in these groups. No significant difference was observed between the groups in terms of tissue damage and cellular degeneration in the corpus of the stomach tissues. (Figure-4A-F and Figure-6C). It was noticed that some intestinal villus cells in duodenum became hypertrophic and there was in places cytoplasmic vacuolization in the PD+K252a group (1.57±0.78) than the control group (0.28±0.48). General histological structure of K252a (0.28±0.48), PD (0.42±0.53), PD+NaHS (0.57±0.53) and PD+NaHS+K252a (0.57±0.53) groups were similar to the control group (Figure-5A-F and Figure-6D).

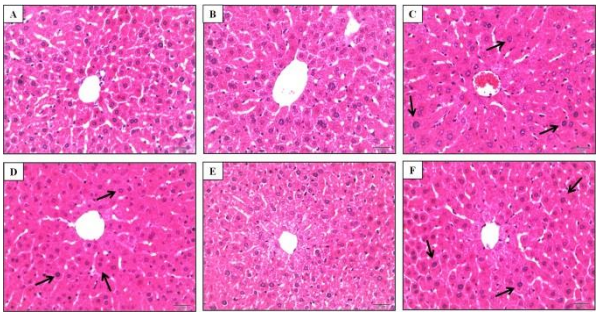

Figure-2. Liver, H-E staining, 40 × magnification. **(A)** Control group, **(B)** K252a group, **(C)** PD group, **(D)** PD+K252a group, **(E)** PD+NaHS group, **(F)** PD+NaHS+K252a group. Arrows indicate degenerated hepatocytes.

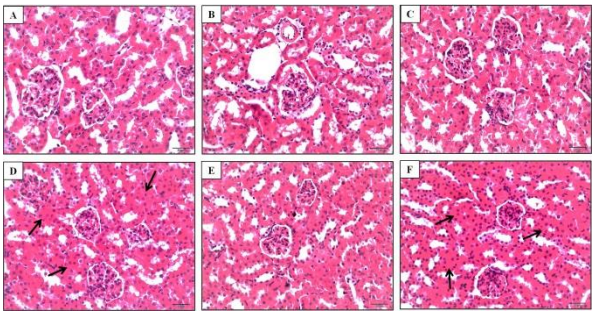

Figure-3. Kidney, H-E staining, 40 × magnification. **(A)** Control group, **(B)** K252a group, **(C)** PD group, **(D)** PD+K252a group, **(E)** PD+NaHS group, **(F)** PD+NaHS+K252a group. Arrows indicate degenerated renal tubules.

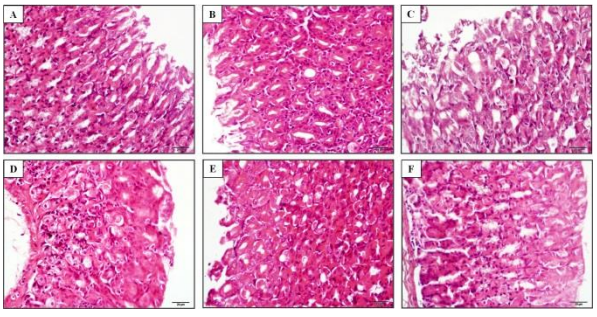

Figure-4. Stomach, H-E staining, 40 × magnification. **(A)** Control group, **(B)** K252a group, **(C)** PD group, **(D)** PD+K252a group, **(E)** PD+NaHS group, **(F)** PD+NaHS+K252a group.

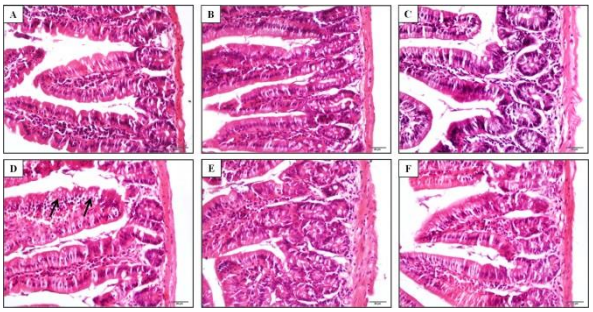

Figure-5. Intestine, H-E staining, 40 × magnification. **(A)** Control group, **(B)** K252a group, **(C)** PD group, **(D)** PD+K252a group, **(E)** PD+NaHS group, **(F)** PD+NaHS+K252a group. Arrows indicate degenerated intestinal villus cells.

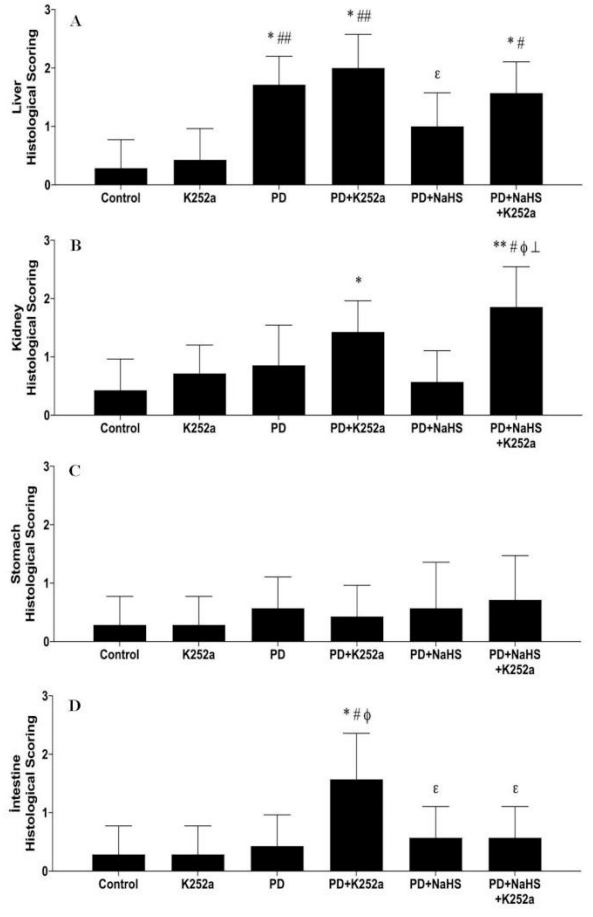

Figure-6. Histological scoring graph for tissue damage and cellular degeneration. **(A)** Liver (difference from control *p<0.0001, K252a #p<0.01, ##p<0.001, PD+K252a εp<0.01), **(B)** Kidney (difference from control *p<0.05, **p<0.001, K252a #p<0.01, PD ϕp<0.05, PD+NaHS ⊥p<0.01), **(C)** Stomach, **(D)** Intestine (difference from control *p< 0.01, K252a #p<0.01, PD ϕp<0.01, PD+K252a εp<0.05).

Biochemical Analyses Results

The liver TAS levels were significantly lower in the PD (0.08±0.09 mmol/L) and PD+K252a (0.12±0.05 mmol/L) groups compared to the control group (0.42±0.11 mmol/L). Sodium hydrosulfite administration alone brought liver TAS levels closer to control in animals with Parkinson's (0.32±0.06 mmol/L), while co-administration of NaHS and K252a (0.22±0.04 mmol/L) significantly prevented the reduction of TAS levels. It was found that liver TOS values in MPTP-treated mice (3.69±0.94 µmol/L) were similar to control (2.75±0.75 µmol/L) and K252a (2.94±1.44 µmol/L) groups. However, TOS level was significantly higher in the PD+K252a group (6.74±0.40 µmol/L). Application of NaHS to PD (3.69±0.94) and PD+K252a (5.53±0.23 µmol/L) groups did not cause a significant reduction in TOS levels (Figure-7).

Renal TAS results did not differ significantly among the groups. TOS values were similar in the control (4.72±0.36 µmol/L), K252a (4.50±0.38 µmol/L), PD (4.42±1.52 µmol/L) and PD+NaHS (4.92±0.73 µmol/L) groups. On the other hand, administration of TrkB receptor antagonist to Parkinson's mice significantly increased renal TOS levels (6.26±0.61 µmol/L). Co-administration of NaHS and K252a in animals with PD (6.77±0.47 µmol/L) did not significantly alter TOS levels (Figure-8).

Gastric TAS results did not differ significantly among the groups. It was found that gastric TOS levels in the experimental groups administered MPTP neurotoxin (1.65±0.35, 1.72±0.10, 1.70±0.23 and 1.74±0.17 µmol/L, respectively) were significantly increased compared to the control group (1.01±0.27 µmol/L). In these groups, administration of K252a and NaHS did not further affect gastric TOS values (Figure-9).

Intestinal TAS values were observed to be significantly lower in all experimental groups compared to the control group. The decrease in antioxidant level was greatest in the PD+K252a group (1.33±0.20 mmol/L). Total oxidant status levels in K252a (0.86±0.13 µmol/L) and PD (0.99±0.06 µmol/L) groups were similar to the control group (0.80±0.15 µmol/L). Administration of TrkB receptor antagonist to mice with PD (1.74±0.45 µmol/L) significantly increased TOS level in intestinal tissue compared to control group, while the administration of NaHS (0.66±0.14 µmol/L) statistically decreased intestinal TOS level. However, it was determined that the application of NaHS in the PD group (0.86±0.27 µmol/L) did not affect the result compared to the PD group (Figure-10).

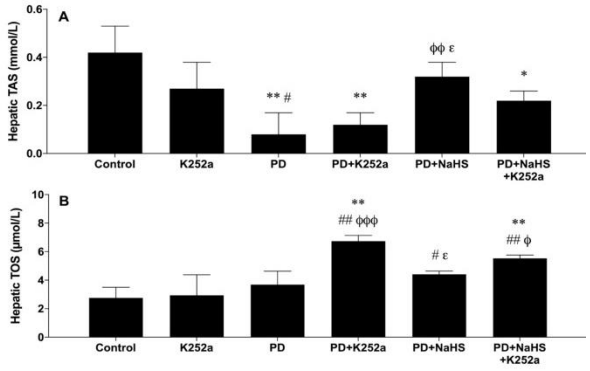

Figure-7. Hepatic **(A)** TAS and **(B)** TOS graphs of control and experimental groups (difference from control *p<0.01, **p<0.001, K252a #p<0.05, ##p<0.01, PD ϕp<0.05, ϕϕp<0.01, ϕϕϕp<0.001, PD+K252a εp<0.01).

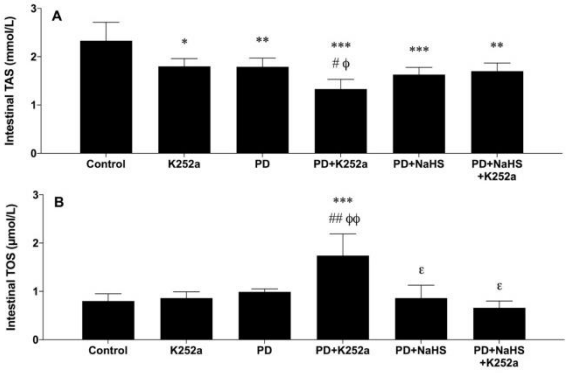

Figure-10. Intestinal **(A)** TAS and **(B)** TOS graphs of control and experimental groups (difference from control *p<0.05, **p<0.01, ***p<0.001, K252a #p<0.05, ##p<0.001, PD ϕp<0.05, ϕϕp<0.001, PD+K252a εp<0.001).

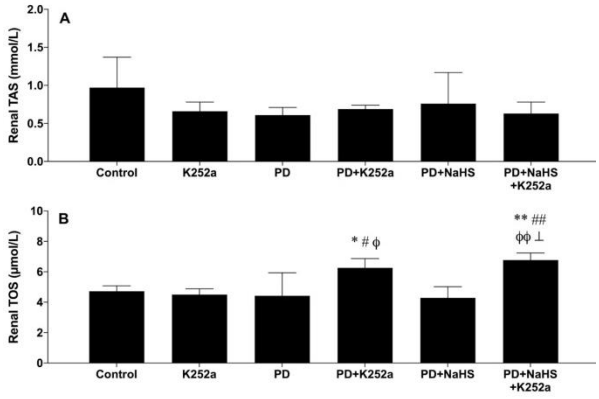

Figure-8. Renal **(A)** TAS and **(B)** TOS graphs of control and experimental groups (difference from control *p<0.05, **p<0.01, K252a #p<0.05, ##p<0.01, PD ϕp<0.05, ϕϕp<0.01, PD+NaHS ⊥p<0.05).

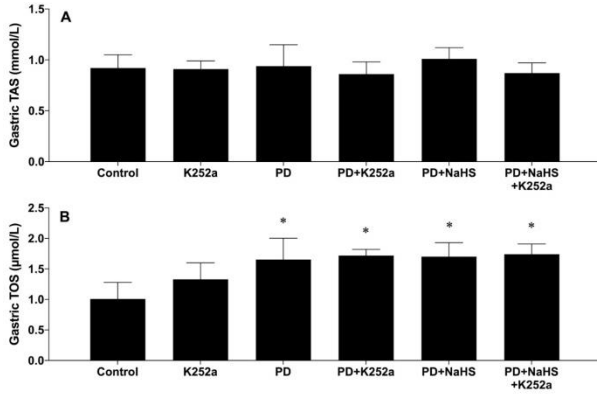

Figure-9. Gastric **(A)** TAS and **(B)** TOS graphs of control and experimental groups (difference from control *p<0.01).

DISCUSSION

Based on the results of our previous study in which we examined the effects of H_2S on nerve damage in PD, and the role of the BDNF-TrkB pathway, we investigated the BDNF-related effects of H_2S on liver, kidney, stomach and intestinal tissues using different methods.

C57BL/6 mice that we used in our study are more sensitive than other rodents to the systemically administered MPTP neurotoxin, which causes PD by selectively destroying dopaminergic neurons in the SN region of the brain (22, 23). Consistent with the literature (20, 24), the presence of bradykinesia and poor motor performance and coordination observed in motor behavior tests in mice in the PD group demonstrated that the PD model was successfully established. Treatment with NaHS increased the success in motor behavior tests, this result proves that H_2S prevents deterioration in motor skills.

Endogenous production of H_2S is mediated primarily by cystathione β-synthase, cystathione γ-lyase, and 3 mercaptopyruvate sulfurtransferase. These enzymes are widely expressed in liver and kidney tissues and regulate hepatic and renal functions (25, 26). Long-term treatment with NaHS has been shown to prevent ROS generation and kidney damage through inhibition of apoptosis and inflammation. Therefore, it has been suggested that NaHS can be considered as a complementary therapeutic agent in protecting against kidney damage (27). In our study, the presence of oxidative stress in the liver tissue of mice with PD was demonstrated by a significant decrease in TAS level, a slight increase in TOS level, and

histologically cellular degeneration signs. It has been concluded that H_2S can have an effect by increasing the basal antioxidant capacity in the liver, since a one-month NaHS administration reduced cellular degeneration, eliminated the decrease in TAS, but did not cause a significant change in TOS level. Because the hepatic TAS and TOS levels were not affected when K252a was given alone, it was realised that endogenous BDNF did not have a significant effect on hepatic oxidative stress in basal conditions. However, the presence of oxidative stress signs in the PD+K252a group and while the TAS value in this group was not different from the PD group, the high TOS value suggested that endogenous BDNF may also be protective against hepatic oxidative stress under stress/damage situations. The fact that there was no statistical difference between the PD+K252a and the PD+NaHS+K252a groups in terms of histological evaluation and oxidative stress, was interpreted as no significant protective effect of H_2S for the liver in these conditions.

In kidney tissue, different from other experimental groups, the presence of cellular degeneration and significantly increased TOS levels were found in the PD+K252a group compared to the control group. This result, similar to the one recorded in the liver, suggested that endogenous BDNF may be protective against renal oxidative stress, especially under stress conditions such as MPTP, although not in basal conditions. The fact that the TOS level in the PD+NaHS+K252a group was not different from the PD+K252a group demonstrated that H_2S was not protective in the kidney. In the PD+NaHS group neither oxidative stress nor histological structure was different from the control or PD group. Contrary to literature findings showing that H_2S is protective in gentamicin-induced kidney injury (27), it does not seem to have any effect on oxidative stress or tissue morphology in the kidneys of subjects with PD. This may be due to the fact that the cellular responses given in different injury models are not the same. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration may have caused a downregulation or inhibition of cellular pathways that mediate the action of H_2S in kidney tissue.

As a result of clinical and experimental studies, it has been understood that H_2S can show mostly proinflammatory, but also anti-inflammatory effects on the intestinal mucosa. It has been stated that endogenously produced H_2S is a prosecretory neuromodulator and a relaxing agent for intestinal contractility (28). As a result of our research, it was determined that MPTP, K252a and NaHS did not cause any histological difference in the stomach, and the administration of MPTP and K252a separately or together did not change TAS, but increased TOS in groups with a PD model. There was no evidence that NaHS was protective in the stomach. Intestinal tissue differed from other peripheral tissues we studied in terms of its sensitivity to both endogenous BDNF and exogenous H_2S. The decrease in TAS in the group given K252a alone, shows that endogenous BDNF is effective in this tissue even under basal conditions and exhibit a contribution to basal antioxidant defense. Compared to PD and K252a groups TAS level was lower and TOS level was higher in PD+K252a group. There was also cellular degeneration in this group. These results show that BDNF plays a protective role against oxidative stress in the intestine in both basal and PD conditions and becomes more susceptible to damage when its effect is inhibited. Exogenous H_2S seems to have no effect in PD-induced subjects, as oxidative stress and histological structure in the PD+NaHS group were not different from the control or PD group. However, the fact that the oxidative stress in the PD+NaHS+K252a group was significantly lower compared to the PD+K252a group was interpreted as that H_2S was protective for the intestinal tissue in these conditions and TrkB receptors had no role in this protective effect.

CONCLUSION

This study, in which we revealed for the first time using biochemical and histological data how peripheral organs are affected in the acute PD model and the protective role of BDNF and H_2S in this process against oxidative stress, sheds light on our better understanding of PD from different aspects. Experimental model of Parkinson's induced by MPTP and inhibition of the BDNF-TrkB pathway caused cellular changes in the liver, kidney, and intestine indicating oxidative stress-induced degeneration. Endogenous BDNF was found to be protective against oxidative stress in liver, kidney, and intestine. It was revealed that NaHS protects the histological structure especially in liver and intestinal tissue and supports the process by increasing the antioxidant capacity in the liver and decreasing the oxidant capacity in the intestine. It was observed that the stomach was not affected by these agents.

Conflict of interest: The authors declare no conflict of interest.

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