Possible effects of rosuvastatin on noise-induced oxidative stress in rat brain

Alevtina Ersoy, Emine Rabia Koc[1], Semsettin Sahin[2], Ulkuhan Duzgun[3], Burcu Acar[3], Atilla Ilhan[4]

Department of Neurology, Mengücek Gazi Training and Research Hospital, Erzincan, Turkey, [1]Department of Neurology, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey, [2]Department of Biochemistry, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey, [3]Department of Neurology, Faculty of Medicine, Turgut Özal University, Ankara, Turkey, [4]Department of Neurology, Faculty of Medicine, Gazi University, Ankara, Turkey

Abstract

The problem of noise has recently gained more attention as it has become an integral part of our daily lives. However, its influence has yet to be fully elucidated. Other than being an unpleasant stimulus, noise may cause health disorders through annoyance and stress, including oxidative stress. Rosuvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, may possess antioxidant properties. Based on rat models, our project investigates the effect of rosuvastatin on noise-induced oxidative stress in the brain tissue. Thirty-two male Wistar albino rats were used. The rats were divided into four groups: Noise exposure plus rosuvastatin usage, only noise exposure, only rosuvastatin usage, and control. After the data had been collected, oxidant and antioxidant parameters were analyzed in the cerebral cortex, brain stem, and cerebellum. Results indicated that superoxide dismutase values were significantly decreased in the cerebral cortex, while malondialdehyde values in the brainstem and cerebellum were significantly increased in the group with only noise exposure. Superoxide dismutase values in the brainstem were significantly increased, but nitric oxide values in the cerebellum and brainstem and malondialdehyde values in the cerebellum and cerebral cortex were significantly decreased in the group where only rosuvastatin was used. During noise exposure, the use of rosuvastatin caused significantly increased superoxide dismutase values in the cerebral cortex and brainstem, but significantly reduced malondialdehyde values in the brain stem. Consequently, our data show that brain tissue was affected by oxidative stress due to continued exposure to noise. This noise-induced stress decreases with rosuvastatin therapy.

Keywords: *Brain, noise, oxidant/antioxidant parameters, oxidative stress, rosuvastatin*

Introduction

Noise is a common problem today in the workplace, entertainment areas, and industry. Although technology is an important part of modern times and makes life easier, it often brings harmful side effects, including noise.

Increasing evidence also suggests that continuous exposure to loud noise releases an excessive amount of free oxygen radicals, which induce tissue damage.[1,2] Oxidative stress, a condition of an imbalance between the oxidant and antioxidant defense systems, is an important factor in the pathogenesis of neurological disorders because the nervous system has a high content of polyunsaturated membrane lipids.[3]

Studies on the antioxidant effects of drugs have become substantially significant, as oxidative stress is regarded as the underlying cause of several diseases. Statins generally have been widely used to reduce cholesterol levels, and recently, they have attracted even more attention due to their antioxidant, anti-inflammatory, anti-ischemic, and blood-brain barrier repairing effects.[4-6] Rosuvastatin is a new-generation inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase; its beneficial effects are independent of serum cholesterol reduction, as it also upregulates antioxidant defense mechanism and prevents tissue damage.[7-9] There are many studies in the literature showing that the auditory, the auditory pathways, and brain can be damaged by exposure to environmental noise.[10-13] However, the effects of statins on cerebral oxidative damage induced by noise have not been investigated to date. Therefore, we decided to determine in this study whether

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noise results in oxidative stress in rat brain tissue, as well as examine the possible effect of rosuvastatin.

Methods

The investigation was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the United States National Institutes of Health (NIH Publication no. 85-23, revised 1996), and approval was received from the Institutional Animal Ethics Committee at Fatih University.

Animals

Thirty-two male Wistar rats (220 ± 20 g) were maintained at a temperature of 22 ± 2°C and relative humidity of 65-70% controlled on a 12-h light-dark cycle. Rats were fed *ad libitum* with commercially available rat chow and water. The animals were housed as eight animals per cage (dimensions of the cage 50 × 35 × 20 cm). The rats were obtained from the laboratory animals department of the medical faculty of the university.

Groups

To allow the rats to get used to the new environment, they were randomly placed in four groups (eight rats per group), 2 weeks before the experiment commenced, as follows:
Group 1: Control. Without noise exposure, the rats were given 1 mg of distilled water through intragastric gavage every day for a period of 30 days.
Group 2: Without noise exposure, these rats were given 10 mg/kg of rosuvastatin (Crestor; Astra Zeneca, Shionogi and Co. Ltd., Osaka, Japan) through intragastric gavage for 30 days.
Group 3: These rats were exposed to 100 dB (A) noise for 4 h/day for 20 days. Beginning 10 days prior to the noise exposure, they were given 1 ml of distilled water through intragastric gavage every day for 30 days.
Group 4: These rats were exposed to 100 dB (A) noise for 4 h/day for 20 days. Beginning 10 days prior to the experiment, they were given 10 mg/kg rosuvastatin through intragastric gavage every day for 30 days.

Noise exposure

White noise was obtained from a broadband noise CD (whitenoisemp3s.com/free-white-noise). It was intensified using a 40-W amplifier and was transmitted from speakers placed 30 cm away from the cage. The intensity of the noise was continuously measured by a sound level meter (sound level meter DT-8850; Shenzhen Technology Co. Ltd., Shenzhen, Guangdong, China). The basal standard noise level and exposure noise level were adjusted to 45 dB (A) and 100 dB (A), respectively. The intensity of 100 dB (A) was chosen because it reflects the common noise level in industrial workplaces and entertainment centers (e.g. dance clubs).

Preparation of tissue samples and the biochemical study

At the end of the experiment, the rats were fasted overnight. The next day, under intraperitoneal anesthesia with ketamine 100 mg/kg and xylazine 4 mg/kg, they were sacrificed by the method of exsanguination from the inferior vena cava. After being sacrificed, the rats were quickly decapitated, and brain tissue samples were taken for biochemical analysis. Then, the specimens were washed free of contaminating blood with ice-cold buffered saline. The tissue samples were divided into three parts: Cerebral cortex, brain stem, and cerebellum. They were placed in aluminum foil and immediately kept in the refrigerator at − 80°C (Sanyo Ultra Low, Osaka, Japan).

For biochemical analysis, the brain tissues were taken from the deep freezer and homogenized in five volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4) for 2 min at 13,000 rpm with a homogenizer (Ultra Turrax Type T-25-B; İKA Labortechnik, Staufen, Germany). The malondialdehyde (MDA) and nitric oxide (NO) measurements were made at this stage. Then, the homogenates were centrifuged for 1 h at 5000 × *g* and the clear upper supernatant fluid was taken. All preparation procedures were performed at + 4°C. To assess oxidative stress in the obtained homogenates and supernatant, we used the commercial chemicals supplied by Sigma (St. Louis, MO, USA) for spectrophotometric identification of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), NO, and MDA levels.

Protein determination

Tissue protein was measured spectrophotometrically according to the method of Lowry *et al*.[14] All samples were assayed in duplicate.

Determination of superoxide dismutase activity

Total (Cu–Zn and Mn) SOD (EC 1.15.1.1) activity was determined according to the method of Sun *et al*., with a slight modification by Durak *et al*.[15,16] The principle of the method is based on the inhibition of nitroblue tetrazolium (NBT) reduction by the xanthine/XO system as a superoxide generator. One unit of SOD was defined as the quantity of the enzyme causing 50% inhibition in the NBT reduction rate. Activity was expressed as units per milligram protein.

Determination of glutathione peroxidase activity

GSH-Px activity was measured by the method of Paglia and Valentine.[17] The enzymatic reaction in a tube containing reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), reduced glutathione, sodium azide, and glutathione reductase was initiated by the addition of H_2O_2, and the change in absorbance at 340 nm was monitored by a spectrophotometer. Enzyme activities were reported as units per gram protein in the brain tissue.

Malondialdehyde determination

The MDA level was determined by the method of Esterbauer.[18] This method is based on the reaction with thiobarbituric acid (TBA) at 90-100°C. In the TBA test reaction, MDA or MDA-like substances and TBA react together to produce a pink pigment with a maximum absorption at 532 nm. The reaction was performed in pH 2-3 at 90°C for 15 min. After cooling, the absorbance was read at 532 nm. The results were expressed as nanomoles per gram protein in wet brain tissues.

NO determination

As NO measurement is very difficult in biological specimens, tissue nitrite and nitrate were estimated as an index of NO production according to the method of Cortas *et al*.[19] This method for brain nitrite and nitrate levels was based on the Griess reaction. Samples were initially deproteinized with Somogyi reagent. Total nitrite (nitrite + nitrate) was measured after conversion of nitrate to nitrite by copperized cadmium granules using a spectrophotometer at 545 nm. Results were expressed as micromoles per gram of wet tissue.

Statistical analysis

Data were expressed as means ± standard deviation (SD). Statistical analyses were carried out by analysis of variance (ANOVA) followed by appropriate *post-hoc* tests, including multiple comparison tests [least significant difference (LSD)].

The Kruskal-Wallis one-way analysis of variance by ranks was used for a simultaneous statistical test of the histopathologic score distribution in the groups. When the null hypothesis could be rejected, comparisons between controls and other groups were made with the Mann-Whitney non-parametric test for independent samples. All analyses were made using the SPSS statistical software package and P values < 0.05 were considered significant.

Results

Tissue oxidant parameters

NO values in the brainstem were found to be significantly lower in group II compared to group III ($P = 0.005$). Without showing a significant difference between the other groups, an increase in NO value was observed in group III compared to group I. NO level in the cerebellum was remarkably lower in group II, compared to groups I, III, and IV ($P = 0.001$, $P = 0.002$, and $P = 0.012$, respectively). Although there was no significant difference between the groups, NO was higher in groups III and IV and lower in group II when compared to group I. Moreover, in the same tissue, NO values were higher in group IV compared to group III [Figure 1].

MDA values observed in the brainstem were higher in group III compared to groups I, II, and IV ($P = 0.000$, $P = 0.008$, and $P = 0.02$, respectively). MDA values were found to be higher in group IV compared to group II ($P = 0.019$). Cerebellar MDA levels were lower in group II compared to groups III and IV ($P = 0.001$ and $P = 0.001$, respectively). MDA levels were found to be significantly higher in groups III and IV in comparison to group I ($P = 0.013$ and $P = 0.016$, respectively). MDA levels in the cerebral cortex were noticeably lower in group II compared to groups I, III, and IV ($P = 0.004$, $P = 0.018$, and $P = 0.011$, respectively). There was no difference in terms of statistical evaluation between the other groups [Figure 2].

Tissue antioxidant parameters

SOD values of the cerebral cortex were found to be lower in group III compared to group I ($P = 0.005$). Moreover, SOD values of the cerebral cortex were remarkably higher in group IV in comparison to groups II and III ($P = 0.004$ and $P = 0.002$, respectively). The rat brainstem SOD levels were found to be higher in groups II and IV compared to group I ($P = 0.002$ and $P = 0.000$, respectively). Additionally, SOD levels in group IV appeared to be higher compared to groups III and II ($P = 0.038$ and $P = 0.003$, respectively). There was no statistically significant difference in the SOD values between the groups; however, SOD was found to be higher in group IV compared to the other experimental groups [Figure 3].

There was no statistical difference between the GSH-Px values of the cerebral cortex, brainstem, and cerebellum in the experimental groups. As shown in Figure 4, when only rosuvastatin was given, GSH-Px levels in the brainstem and the cortex increased. However, when rosuvastatin administration was accompanied by exposure to noise, GSH-Px levels in the same tissues exposed to only noise were not affected. While cerebellar GSH-Px levels in group II were similar to those in the control group, the same GSH-Px levels in groups III and IV showed an increase [Figure 4].

Discussion

Noise is considered the second most dangerous environmental factor after air pollution. It significantly affects people, particularly those living in large cities.[20]

At workplaces throughout the world, noise is the most common harmful agent and poses a huge threat. According to the World Health Organization data, 15% of workers are exposed to noise levels that create a health risk.[21] Importantly, noise does not have to be very loud for a person to be affected. Even only as loud as a human voice, noise can result in sleep disorders, neuroendocrine changes at night, and poor performance during the day.[22,23]

In recent years, it has been found that lipid peroxidation increases the amount of free radicals and leads to diseases,

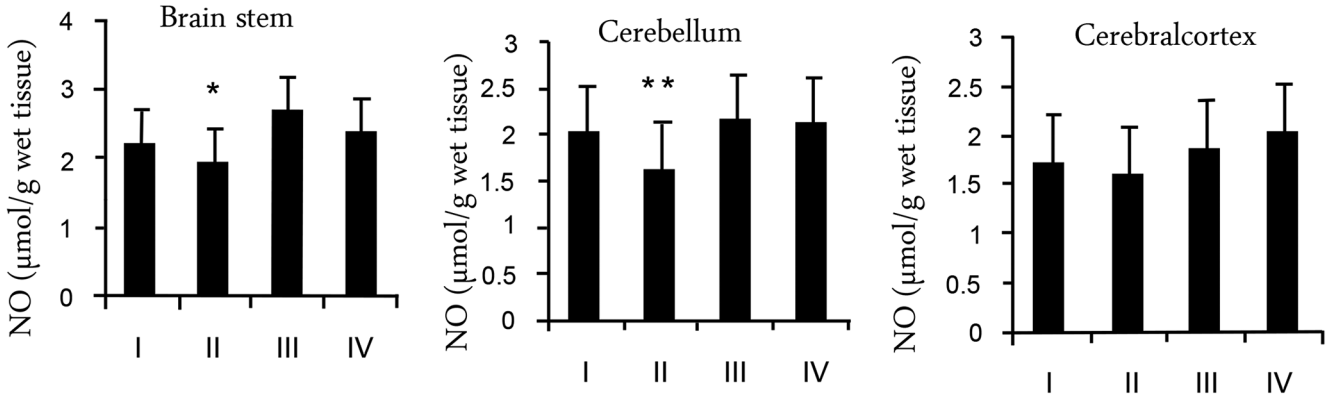

Figure 1: NO activity in brainstem, cerebellum, and cerebral cortex of the rats in each group. **P* = 0.005 vs. group III; ** *P* < 0.012 vs. all other groups (group I: Control, group II: Rosuvastatin usage, group III: Noise exposure, group IV: Noise exposure and rosuvastatin usage)

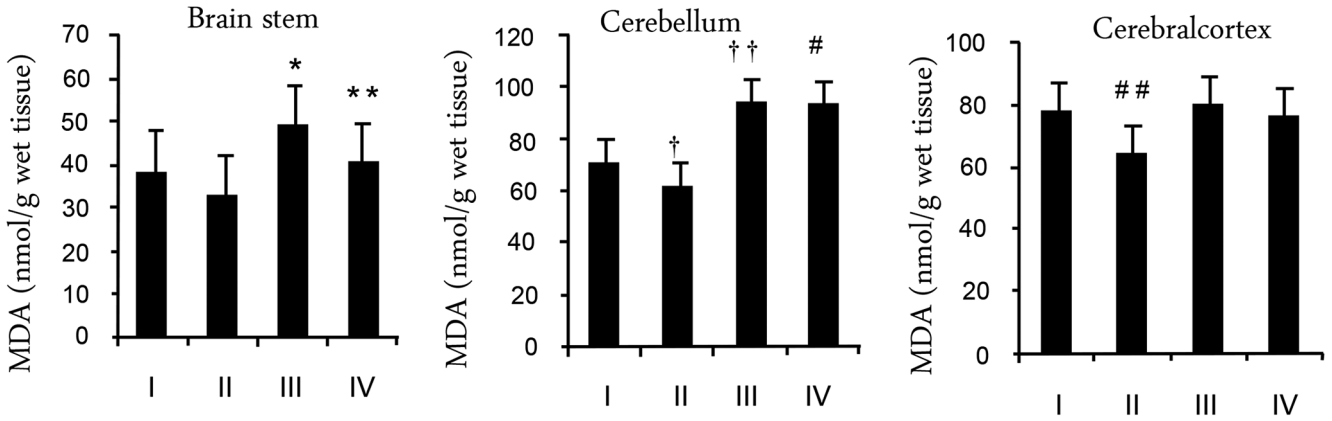

Figure 2: MDA activity in brainstem, cerebellum, and cerebral cortex of the rats in each group. **P* < 0.02 vs. groups I, II, and IV; ***P* = 0.019 vs. group II; †*P* = 0.001 vs. groups III and IV; ††*P* = 0.013 vs. group I; #*P* = 0.016 vs. group I; ##*P* < 0.018 vs. all other groups

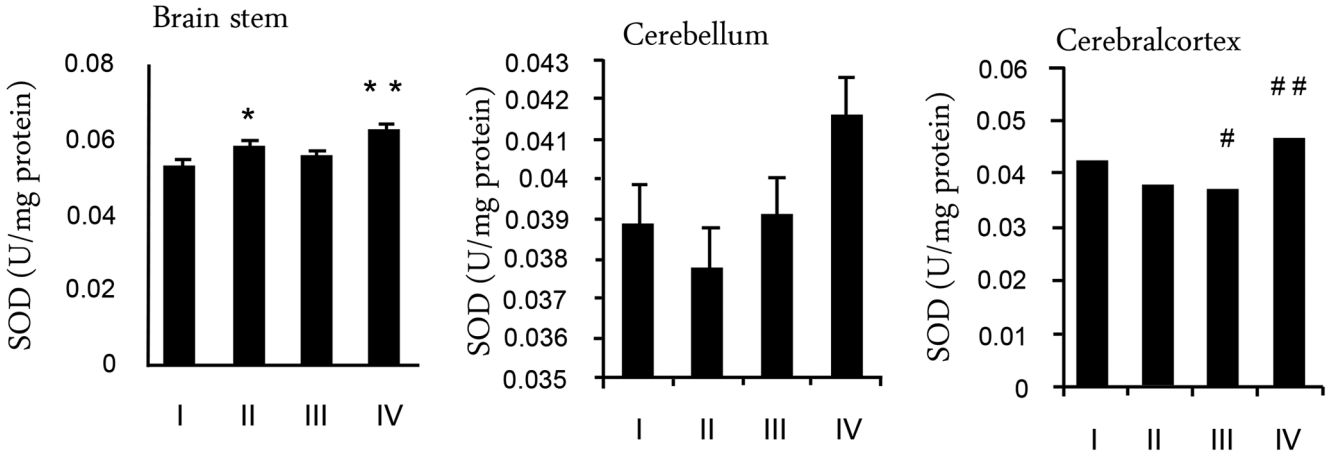

Figure 3: SOD activity in brainstem, cerebellum, and cerebral cortex of the rats in each group. **P* = 0.002 vs. group I; ***P* < 0.038 vs. all other groups; #*P* = 0.005 vs. group I; ##*P* < 0.004 vs. groups II and III

including coronary artery disease, psoriasis, motor neuron disease, Alzheimer's disease, diabetes mellitus, Behcet's disease, various eye and skin diseases, cancer, and aging.[24-27]

Studies also show that noise causes an increase in free oxygen radicals, resulting in oxidative stress. For example, Samson *et al.* have shown that excessive reactive oxygen species (ROS) production during noise exposure causes

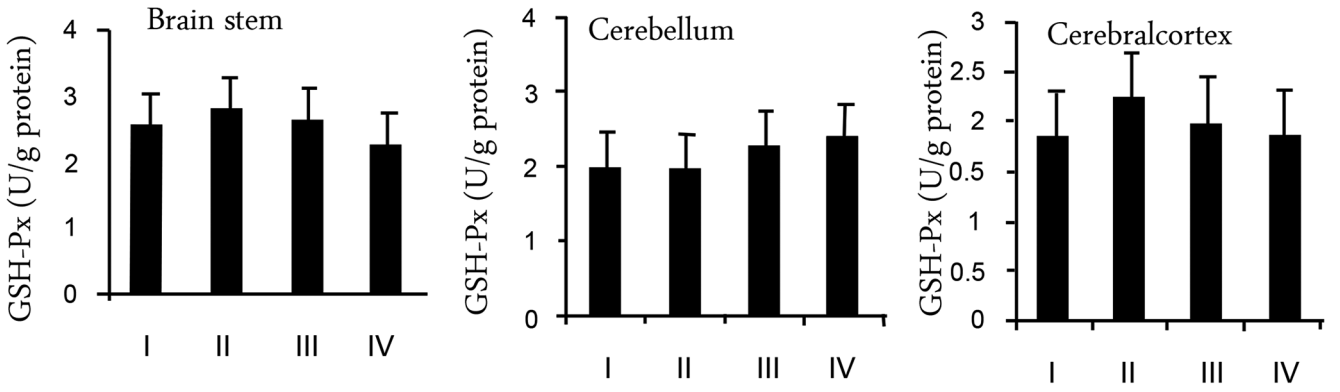

Figure 4: GSH-Px activity in brainstem, cerebellum, and cerebral cortex of the rats in each group

noise-induced hearing loss (NIHL) by affecting the hair cells in the cochlea.[28] Additionally, Fetoni *et al*. found that acoustic trauma altered dendritic morphology and decreased the number of spines of the pyramidal neurons of auditory cortices.[29] In an investigation of the effects of moderate-intensity white noise exposure on learning and memory of mice, Cheng *et al*. determined the levels of oxidative stress in the critical region [e.g. inferior colliculus (IC)], auditory cortex (AC), and hippocampus, which are associated with the acoustic lemniscal ascending pathway. The study results showed evidence of oxidative damage in the IC, AC, and hippocampus.[30] In another study on animals exposed to 120 dB white noise for 2 h, oxidative DNA damage marked by 8-hydroxy-2′-deoxyguanosine (8-OHdG) was detected in the cochlea 1 day later. Damage in the brain and liver was detected 3 days after the exposure.[11] In yet another study, Manikandan *et al.* found increased MDA levels in different areas of the brain after 30 days of 100 dB white noise exposure, and Srikumar and colleagues in their study found increased levels of MDA in the serum, thymus gland, and spleen tissue after a 15-day exposure to white noise.[10,13] Similarly, high levels of lipid peroxidation have been indicated in other studies as an indirect sign of increased ROS production in the serum and different areas of the brain during acute, subacute, and chronic noise exposure.[3,10,31] Our study results are in accordance with these findings, as it found that noise increased MDA levels in the cerebellum and brainstem. This might be attributed to the fact that noise enters the brain from the brainstem, as the auditory nuclei are located in the brainstem.

Another sign of oxidative stress is increased NO levels. While NO has numerous regulating and protective functions, it also has toxic effects that could threaten the function and life of cells. NO is formed in several tissues from arginine as a result of a reaction catalyzed by nitric oxide synthase (NOS).[32] In our study, noise exposure did not cause a statistically significant change in NO levels in the brain tissue, compared to the control group.

As far as is known, the NOS enzyme is inhibited by glucocorticoids.[33] Noise as a stress factor affects the synthesis and secretion of corticosterone, changes the adaptive response of the adrenal cortex, and increases cortisone levels.[23,34,35] Although cortisone levels were not measured in our study, considering the findings of prior studies, we can discuss an increase in these levels and, as a result of this, a failure of increase in NO levels. On the other hand, increased superoxide caused by SOD consumption reacts with NO, and this could cause NO consumption resulting in a failure of increase in its levels.

In previous studies, asymmetric dimethylarginine (ADMA) levels were shown to increase in cases of oxidative stress. It has been declared that ADMA, the endogenous inhibitor of NOS, is high in people with cardiovascular risk factors such as atherosclerosis, diabetes, insulin resistance, hypertension, and hypercholesterolemia. It also suppresses the formation of NO and increases the production of superoxide radicals.[36] In our study, it can be assumed that ADMA activity increased in noise-induced oxidative damage, and therefore, NO levels did not increase.

There are some defense mechanisms to prevent the formation of free radicals and their harmful effects. Several antioxidant enzymes within the framework of the antioxidant defense system enable these mechanisms. The most important of these are SOD, GSH-Px, and catalase (CAT). The main function of the SOD enzyme is to protect cells against the harmful effects of superoxide. Resulting from this reaction, hydrogen peroxide is removed by the CAT and GSH-Px enzymes, which work together with SOD. Several findings, which show both increase and decrease in SOD levels in case of oxidative stress, are available in the literature.[3,10,13] In our study, while the cerebral cortex SOD level of the rats exposed to noise were significantly lower compared to those of the control group, there was no change in brainstem and cerebellum SOD levels. The results we obtained are similar to those of other studies.[37,38] The decrease in SOD activity accompanied by increased lipid peroxidation might be explained by the consumption of antioxidant enzymes developed by the increase in lipid peroxidation. A decrease in SOD levels in a particular area of the brain may indicate that it is more sensitive to noise.

Formed in the reaction catalyzed by SOD, hydrogen peroxide is decomposed into water and oxygen by GSH-Px. Several studies show that in the case of oxidative stress caused by environmental factors, the aforementioned enzyme levels increase or decrease.[3,10,12,13,31,37-39] In our study, noise did not cause a statistically dramatic change in GSH-Px enzyme levels in the brain tissue, compared to the control group. Considering the SOD levels were low, a lack of change in GSH-Px levels could be explained by the low production of hydrogen peroxide developed through SOD consumption.

Rosuvastatin is a new-generation inhibitor of HMG-CoA reductase. It was first developed in Japan in 1998. Although structurally similar to other statins, it is different in terms of formula, pharmacokinetic, pharmacodynamic, and clinical characteristics. Rosuvastatin is a synthetic lipophilic drug with high selectivity for hepatocytes and is a strong inhibitor of HMG-CoA reductase.[40]

Although the 90% lipid-reducing dose of rosuvastatin was reported to be 20 mg/kg/day, we used it at a dose of 10 mg/kg/day for 20 days because 10 mg/kg/day was used in most animal studies.[36]

In our antioxidative profile, in the group where rosuvastatin was given singly, a significant increase in SOD levels was observed in the brainstem. However, in the group where rosuvastatin was given in combination with noise exposure, SOD levels increased significantly in the cerebral cortex and brainstem; however, in the cerebellum, SOD levels increased insignificantly compared to the control group and the group only exposed to noise. Rosuvastatin given singly or to the rats exposed to noise did not significantly affect GSH-Px levels in the brain tissue.

There are only few studies on the effect of rosuvastatin on these enzymes, and their results are contradictory. Study results have shown that the antioxidant effect of rosuvastatin appears to be due to its increasing the expression of the SOD1 enzyme.[7,41] Gomez-Garcia *et al.* have clarified that rosuvastatin treatment leads to an increase in serum SOD levels and a decrease in GSH-Px levels.[42] Other studies reported that rosuvastatin increases GSH-Px levels in the serum.[43]

Studies indicate that the antioxidant effect of rosuvastatin is due to the inhibition of NAD (P) H oxidase and ADMA, which occurs in the formation of the superoxide radical.[39] We believe that by inhibiting these molecules, rosuvastatin may decrease the amount of superoxide radical; as a result, SOD may be insufficiently consumed, and consequently, its level may be increased.

As seen from the results of our study, in the case of oxidative stress, rosuvastatin performs its antioxidant effects on brain tissue by increasing SOD levels, but not by affecting GSH-Px levels. The unchanged GSH-Px levels can be explained by the CAT enzyme decomposing the hydrogen peroxide that is formed due to the increased activity of SOD. These ideas are based on other studies indicating that rosuvastatin increases the activity of the CAT enzyme.[43]

In our study, rosuvastatin given singly led to a decrease of MDA levels, which was significant in the cerebellum and cortex but insignificant in the brainstem. High MDA levels from noise exposure decreased when noise was combined with rosuvastatin and became almost equal to the control group. Similarly, Habibi *et al.* showed in their study that rosuvastatin inhibits lipid peroxidation.[44]

Rosuvastatin was shown to have a regulatory effect on the NOS enzyme, and this effect was reported to be independent of the lipid-decreasing effect.[45] Similarly, we observed that when rosuvastatin was given singly in our study, NO levels were significantly lower compared to the control group only in the cerebellum; in the brainstem and cerebral cortex, they were similar to the control group. In spite of the fact that in noise exposure, rosuvastatin treatment does not significantly change the NO levels in the brainstem and cerebellum, NO levels were found to be lower compared to the group only exposed to noise.

It has been shown that the antioxidant effect of rosuvastatin does not depend on its cholesterol-decreasing properties. However, the inhibition of the regulatory effect of rosuvastatin on the NOS system with mevalonate and the correlation of the inhibition of NAD (P) H oxidase with the inhibition of HMG-CoA reductase suggest that the mevalonate pathway plays a role in the antioxidant activity of rosuvastatin.[43,46,47]

Furthermore, the antioxidant effects of rosuvastatin are claimed to be dose-related. For example, Ajith *et al.* found that rosuvastatin decreased lipid peroxidation in the brain and liver tissue depending on the dose.[46] Laufsa *et al.* showed that there is also a dose-related effect of rosuvastatin on NOS.[4] Based on these studies, we suppose that in our experiment on rats exposed to noise and treated with rosuvastatin, the NO and MDA levels would have been lower and GSH-Px and SOD levels would have been higher in the brain tissue, if we had used a larger dose of rosuvastatin.

As a result, we have demonstrated that noise leads to cerebral oxidative stress and that rosuvastatin treatment reduces the oxidative stress considerably, though not entirely. Rosuvastatin brings about this effect by decreasing lipid peroxidation and NO levels, as well as by increasing SOD activity. Although the above-mentioned effect is not very prominent in certain situations (at a dose of 10 mg/kg/day), we believe it will be more prominent with an increased dosage of rosuvastatin. Thus, in addition to its typical lipid-lowering effect, rosuvastatin can be regarded as a protective alternative due to its protective effect against noise-induced oxidative stress.

Address for correspondence:
Dr. Emine Rabia Koc,
Department of Neurology, Balıkesir Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı,
Çağış Yerleşkesi, 10145 Balıkesir, Turkey.
E-mail: erabiakoc@yahoo.com

References

1. Yildirim I, Kilinc M, Okur E, Inanc Tolun F, Kilic MA, Kurutas EB, *et al*. The effects of noise on hearing and oxidative stress in textile workers. Ind Health 2007;45:743-9.
2. Pouyatos B, Gearhart C, Nelson-Miller A, Fulton S, Fechter L. Oxidative stress pathways in the potentiation of noise-induced hearing loss by acrylonitrile. Hear Res 2007;224:61-74.
3. Samson J, Sheeladevi R, Ravindran R. Oxidative stress in brain and antioxidant activity of Ocimum sanctum in noise exposure. Neurotoxicology 2007;28:679-85.
4. Laufs U, Gertz K, Dirnagl U, Bohm M, Nickenig G, Endres M. Rosuvastatin, a new HMG-CoA reductase inhibitor, upregulates endothelial nitric oxide synthase and protects from ischemic stroke in mice. Brain Res 2002;942:23-30.
5. Stepien K, Tomaszewski M, Czuczwar SJ. Neuroprotective properties of statins. Pharmacol Rep 2005;57:561-9.
6. Zacco A, Togo J, Spence K, Ellis A, Lloyd D, Furlong S, *et al*. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect cortical neurons from excitotoxicity. J Neurosci 2003;23:11104-11.
7. Mahalwar R, Khanna D. Pleiotropic antioxidant potential of rosuvastatin in preventing cardiovascular disorders. Eur J Pharmacol 2013;711:57-62.
8. Ma M, Uekawa K, Hasegawa Y, Nakagawa T, Katayama T, Sueta D, *et al*. Pretreatment with rosuvastatin protects against focal cerebral ischemia/reperfusion injury in rats through attenuation of oxidative stress and inflammation. Brain Res 2013;1519:87-94.
9. Ansari JA, Bhandari U, Pillai KK, Haque SE. Effect of rosuvastatin on obesity-induced cardiac oxidative stress in Wistar rats--a preliminary study. Indian J Exp Biol 2012;50:216-22.
10. Manikandan S, Devi RS. Antioxidant property of alpha-asarone against noise-stress-induced changes in different regions of rat brain. Pharmacol Res 2005;52:467-74.
11. Van Campen LE, Murphy WJ, Franks JR, Mathias PI, Toraason MA. Oxidative DNA damage is associated with intense noise exposure in the rat. Hear Res 2002;164:29-38.
12. Manikandan S, Padma MK, Srikumar R, Jeya Parthasarathy N, Muthuvel A, Sheela Devi R. Effects of chronic noise stress on spatial memory of rats in relation to neuronal dendritic alteration and free radical-imbalance in hippocampus and medial prefrontal cortex. Neurosci Lett 2006;399:17-22.
13. Manikandan S, Srikumar R, Jeya Parthasarathy N, Sheela Devi R. Protective effect of Acorus calamus LINN on free radical scavengers and lipid peroxidation in discrete regions of brain against noise stress exposed rat. Biol Pharm Bull 2005;28:2327-30.
14. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265-75.
15. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem 1988;34:497-500.
16. Durak I, Yurtarslanl Z, Canbolat O, Akyol O. A methodological approach to superoxide dismutase (SOD) activity assay based on inhibition of nitroblue tetrazolium (NBT) reduction. Clin Chim Acta 1993;214:103-4.
17. Paglia DE, Valentine WN. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 1967;70:158-69.
18. Esterbaur H, Cheeseman K. Determination of aldehydic lipid peroxidation products: Malonaldehyde and 4-hydroxynonenal. In: Packer L, Glazer A, editors. Methods in Enzimology V 186 Oxygen Radicals in Biological systems. New York: Academic Press; 1990. p. 407-21.
19. Cortas NK, Wakid NW. Determination of inorganic nitrate in serum and urine by a kinetic cadmium-reduction method. Clin Chem 1990;36:1440-3.
20. Jakovljevic B, Paunovic K, Belojevic G. Road-traffic noise and factors influencing noise annoyance in an urban population. Environ Int 2009;35:552-6.
21. Concha-Barrientos M, Campbell-Lendrum D, Steenland K. Occupational Noise. Environmental Burden of Disease Series, No. 9. World Health Organization. Protection of the Human Environment. Geneva: WHO; 2004.
22. Kishikawa H, Matsui T, Uchiyama I, Miyakawa M, Hiramatsu K, Stansfeld SA. Noise sensitivity and subjective health: Questionnaire study conducted along trunk roads in Kusatsu, Japan. Noise Health 2009;11:111-7.
23. Melamed S, Bruhis S. The effects of chronic industrial noise exposure on urinary cortisol, fatigue and irritability: A controlled field experiment. J Occup Environ Med 1996;38:252-6.
24. Ilkun O, Boudina S. Cardiac dysfunction and oxidative stress in the metabolic syndrome: An update on antioxidant therapies. Curr Pharm Des 2013;19:4806-17.
25. Ozkan Y, Yardım-Akaydın S, Sepici A, Keskin E, Sepici V, Simsek B. Oxidative status in rheumatoid arthritis. Clin Rheumatol 2007;26:64-8.
26. Venkateshappa C, Harish G, Mythri RB, Mahadevan A, Bharath MM, Shankar SK. Increased oxidative damage and decreased antioxidant function in aging human substantia nigra compared to striatum: İmplications for Parkinson's disease. Neurochem Res 2012;37:358-69.
27. Murdolo G, Piroddi M, Luchetti F, Tortoioli C, Canonico B, Zerbinati C, *et al.* Oxidative stress and lipid peroxidation by-products at the crossroad between adipose organ dysregulation and obesity-linked insulin resistance. Biochimie 2013;95:585-94.
28. Samson J, Wiktorek-Smagur A, Politanski P, Rajkowska E, Pawlaczyk-Luszczynska M, Dudarewicz A, *et al*. Noise-induced time-dependent changes in oxidative stress in the mouse cochlea and attenuation by D-methionine. Neuroscience 2008;152:146-50.
29. Fetoni AR, De Bartolo P, Eramo SL, Rolesi R, Paciello F, Bergamini C, *et al*. Noise-induced hearing loss (NIHL) as a target of oxidative stress-mediated damage: Cochlear and cortical responses after an increase in antioxidant defense. J Neurosci 2013;33:4011-23.
30. Cheng L, Wang SH, Chen QC, Liao XM. Moderate noise induced cognition impairment of mice and its underlying mechanisms. Physiol Behav 2011;104:981-8.
31. Demirel R, Mollaoğlu H, Yeşilyurt H, Üçok K, Ayçiçek A, Akkaya M, *et al*. Noise induces oxidative stress in rat. Eur J Gen Med 2009;6:2024.
32. Jung J, Na C, Huh Y. Alterations in nitric oxide synthase in the aged CNS. Oxid Med Cell Longev 2012;2012:718976.
33. Simmons WW, Ungureanu-Longrois D, Smith GK, Smith TW, Kelly RA. Glucocorticoids regulate inducible nitric oxide synthase by inhibiting tetrahydrobiopterin synthesis and L-arginine transport. J Biol Chem 1996;271:23928-37.
34. Spreng M. Noise induced nocturnal cortisol secretion and tolerable overhead flights. Noise Health 2004;6:35-47.
35. Ising H, Braun C. Acute and chronic endocrine effects of noise: Review of the research conducted at the Institute for Water, Soil and Air Hygiene. Noise Health 2000;2:7-24.
36. Kilic E, Kilic U, Matter CM, Luscher TF, Bassetti CL, Hermann DM. Aggravation of focal cerebral ischemia by tissue plasminogen activator is reversed by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor but does not depend on endothelial NO synthase. Stroke 2005;36:332-6.
37. Srikumar R, Parthasarathy NJ, Manikandan S, Narayanan GS, Sheeladevi R. Effect of Triphala on oxidative stress and on cell-mediated immune response against noise stress in rats. Mol Cell Biochem 2006;283:67-74.
38. Ilhan A, Gurel A, Armutcu F, Kamisli S, Iraz M, Akyol O, *et al*. Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain. Clin Chim Acta 2004;340:153-62.
39. Olsson AG, McTaggart F, Raza A. Rosuvastatin: A highly effective new HMG-CoA reductase inhibitor. Cardiovasc Drug Rev 2002;20:303-28.
40. Holvoet P. Relations between metabolic syndrome, oxidative stress and inflammation and cardiovascular disease. Verh K Acad Geneeskd Belg 2008;70:193-219.

41. Gomez-Garcia A, Martinez Torres G, Ortega-Pierres LE, Rodriguez-Ayala E, Alvarez-Aguilar C. Rosuvastatin and metformin decrease inflammation and oxidative stress in patients with hypertension and dyslipidemia. Rev Esp Cardiol 2007;60:1242-9.
42. Shchukin IuV, D'Iachkov VA, Seleznev EI, Danilova EA, Pikatova EA, Medvedeva EA. Molecular mechanisms of effects of rosuvastatin on systemic oxidative stress and endogenous inflammation in patients with atherosclerosis. Kardiologiia 2008;48:41-5.
43. Habibi J, Whaley-Connell A, Qazi MA, Hayden MR, Cooper SA, Tramontano A, *et al*. Rosuvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, decreases cardiac oxidative stress and remodeling in Ren2 transgenic rats. Endocrinology 2007;148:2181-8.
44. Sicard P, Delemasure S, Korandji C, Segueira-Le Grand A, Lauzier B, Guilland JC, *et al*. Anti-hypertensive effects of Rosuvastatin are associated with decreased inflammation and oxidative stress markers in hypertensive rats. Free Radic Res 2008;42:226-36.
45. Piconi L, Corgnali M, Da Ros R, Assaloni R, Piliego T, Ceriello A. The protective effect of rosuvastatin in human umbilical endothelial cells exposed to constant or intermittent high glucose. J Diabetes Complications 2008;22:38-45.
46. Ajith TA, Riji T, Anu V. *In vitro* anti-oxidant and DNA protective effects of the novel 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor rosuvastatin. Clin Exp Pharmacol Physiol 2008;35:625-9.
47. Otto A, Fontaine D, Fontaine J and Berkenboom G. Rosuvastatin treatment protects against nitrate-induced oxidative stress. J Cardiovasc Pharmacol 2005;46:177-84.

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