Original Article

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Effect of Aging and Regular Exercise on Prefrontal Cortex Histopathology, Myelin Density, and Antioxidant Activity of the Rats

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ABSTRACT

Background & Objective: Aging related to decline in physiological structure and functional capacity in brain. The aim of this research was to examine the differences in the pathophysiology of the prefrontal cortex (PFC) region between young and old rats.

Materials & Methods: The young and old male Wistar rats (n= 40) were subgroups to normal young (NY), exercise young (EY), normal old (NO) and exercise old (EO). A forced aerobic exercise (FAE) program was established using a treadmill for 12 weeks. The exercise program including a turn off treadmill for normal groups while a turn on treadmill at a speed of 10-12 m/min for exercise groups. Toluidine blue and Cresyl-violet staining were used to evaluation of volume white matter (WM) and dark cell numbers in the prefrontal cortex (PFC). Levels of glutathione peroxidase (GPx) and malondialdehyde (MDA) were measured by spectrophotometric and Satoh methods, respectively. Afterward, the percentage of myelin basic protein (MBP) was assessed using immunohistochemical staining.

Results: Our findings revealed a significant enhancement in the mean percentage of WM area, percentage of MBP and level of GPx in EO group compared to NO group ($P \leq 0.05$). Also, the dark cell number and MDA level decreased in the old rats with exercise compared to NO group ($P \leq 0.05$). However, there was no significant difference between other groups ($P \geq 0.05$).

Conclusion: The results indicated that normal aging has destructive effects on the PFC and antioxidants rate. However, the regular exercise with specialized program could improve deteriorate changes of aging on brain.

Keywords: Aging, Prefrontal cortex, White matter, Exercise

Introduction

The aging process has substantial implications for the body function and results in a decline of the vascular system **(1, 2)** . Hence, the brain undergoes neuronal loss in the cerebral cortex and shows synaptic damage in some areas, which may have a detrimental effect on cognitive behaviors **(3).** Based on age-associated white matter (WM) area changes in the brain, some investigations suggest that WM deterioration begins primarily in late adulthood with these damages becoming maximal in old age **(4, 5)**.

Furthermore, the aging process involves damage by oxidative stress, free radicals, inflammation, mitochondrial dysfunction, telomere destruction, as well as impaired DNA repair and defects in tissue

regeneration **(6, 7)**. Since the brain is more vulnerable than other organs, oxidative stress has a substantial impact on typical brain function, whereby the brain uses up extensive oxygen and increases the abundance of free radicals such as malondialdehyde (MDA) **(8)**. Although there are antioxidant protection system such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in the brain, which act as preventive factors against oxidative damage **(9)**, the aging increases the amount of polyunsaturated fatty acids and reduces the antioxidant ability in the brain compared to other tissues **(10)**. Thus, many normal age-related biological changes occur even in the absence of dementia and other degenerative conditions in the brain especially in frontal and temporal lobes **(11)**. However, inconsistent changes in the prefrontal cortex (PFC) area have been reported **(12, 13)**. Also, there is limited evidence regarding age-associated alterations in the microstructure of cerebral WM **(14).** In addition, myelin maturation is limited in aging. Myelin is primarily made up from multiple proteins, including myelin basic protein (MBP), providing about 30% of all myelin proteins **(15)**. Since myelin is involved in cortical neurodegeneration, neuroplasticity, and neuroinflammation, it has recently attracted the attention of many researchers **(16)**.

The aging has side effects on the brain tissue; meanwhile, exercise has been proposed as an approach to reduce the complications of aging. In the elderly, regular physical exercise increases local cerebral blood flow in several important areas of the brain and the response to cognitive functions **(17)**. It can also reduce the risk of cognitive defects and dementia in future life **(18)**.

Hence, the aim of this study was to evaluate the effects of aerobic exercise training on WM histopathological changes, amounts of oxidative stress, and level of antioxidants in the PFC of aged rats.

Materials and Methods

Materials

Toluidine blue (89640) and cresyl violet acetate (C1791-5g) were purchased from Sigma Chemical Co Saint Louis, Missouri USA. GPx and MDA kits were received from Randox, UK. The goat polyclonal secondary antibody to mouse IgG (FITC) and the goat serum were ab6785 and ab7481, respectively.

Animals

Twenty young male Wistar rats (2 months old, 250–320 g) and 20 old male Wistar rats (18 months old, 350-400 g) were obtained from the animal lab at Iran University of Medical Sciences. Then, animals were housed under controlled light and environmental conditions (12hr light/12hr dark cycle and enough food and water). This study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (Grant no. 393236).

Each group was divided into two subgroups: normal and exercise. The young animals were normal young (NY) and exercise young (EY). Similarly, the older animals were normal old (NO) and exercise old (EO). The normal groups were placed 10 minutes daily on a turned off treadmill, while animals in the exercise groups were subjected to daily forced aerobic exercise (FAE). In the exercise groups, rats underwent seven days of habituation to daily running sessions on a motor-driven treadmill (Pishroo Andisheah Senate, A1400Y10, Iran) with a speed of 10-12 m/min. The procedures were performed for 12 weeks (5 d/week). During this period, both time and speed were increased slowly until the rats were able to run for 1hr at 22 m/min daily in the 12th week **(19)**. Table 1 reports the exercise protocol during 12 weeks.

Table 1. The exercise programming during 12 weeks

Week	Interval group	Rest (min)
1	2× (5-8min) × (12 m/min)	2.30-4
2	2 × (8-9min) × (12 m/min)	4
3	2 × (10-12min) × (13m/min)	4.30-5
4	2 × (12-14min) × (14m/min)	5-6
5	3 × (10-12min) × (15m/min)	4.30-5
6	3 × (12-14min) × (16m/min)	5-6
7	3 × (15-17min) × (17m/Min)	6.30-8
8	3 × (17-19min) × (18m/min)	8-8.30
9	4 × (15-17min) × (19m/min)	6.30-8
10	4 × (17-19min) × (20m/min)	8-9
11	4 × (20min) × (21-22m/min)	9
12	4 × (20min) × (22-23m/min)	9

Histological Analysis

After the last exercise session, animals were anesthetized using ketamine (150 mg/kg) and xylazine (15 mg/kg), followed by perfusion by 4% paraformaldehyde in a 0.1 M phosphate buffer saline (PBS). Following perfusion, the brain was removed and fixed. After tissue processing, the specimens were sectioned at a thickness of 4 µm (Bergma 1.3 mm to 4.3 mm) from the coronal plane and stained with Toluidine blue plus Cresyl-violet staining for evaluating WM area and counting dark cells, respectively (20, 21). Then, five sections from the PFC were analyzed by a microscope at 4× magnification. For analysis of the WM, the slide was studied using Image-j software.

Immunohistochemical Myelin Basic Protein (MBP) Staining

In this study, MBP was used as a myelin sheath marker. The serial sections with 4 µm thickness of brain were mounted on slides. Then, immunohistochemical staining for MBP were performed as described in a previous study. Rabbit anti mouse FITC (1:400 dilution) was used as secondary antibodies. Subsequently, all sections were stained with the nuclear dye, 4,6-diamidino-2-phenylindole (DAPI), whereby immunohistochemistry results were observed under a fluorescent microscope (Olympus BX51, Japan). Then, the total area of the images was measured to assess the intensity of MBP staining (22).

Antioxidant Activity Detect

After FAE program period, the rats were anesthetized and killed by decapitation. Brains were immediately removed. The PFC was isolated and washed in an ice-cold phosphate buffer saline (PBS). They were then immediately immersed in liquid nitrogen and stored at -80°C until biochemical analysis for GPx enzyme activity and MDA.

GPx activity was determined using the spectrophotometric method (23). The enzyme activity was calculated based on the oxidized nicotinamide adenine dinucleotide phosphate (NADP). The absorbance measurements were taken at a wavelength of 340 nm. MDA is used as a standard measurement for oxidation level damaged by free radicals. The MDA process was determined by the Satoh method (24), which was used to measure the color produced by the thiobarbituric acid (TBA) and MDA reaction. The supernatant of the PFC was precipitated by trichloroacetic acid (TCA) with the mixture heated by a TBA in 2 M sodium sulfate, in a boiling water bath for 30 min. After extracting the resulting chromogenic with n-butyl alcohol, the sample absorbance was measured at 530 nm wavelength. MDA levels were expressed as nm/mg of protein.

Statistical Analysis

The findings were expressed as the mean ± standard error (SEM). Statistical analysis was carried out using SPSS version 26. Statistical comparisons among groups were performed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test where a P-value < 0.05 was considered statistically significant.

Results

White Matter Area

The results revealed that there was a significant difference in the mean percentage of the WM area of the PFC between the different groups **(Figure 1)**. NO group had a significantly lower mean percentage of the WM area compared to the NY group (P=0.035). Also, the mean percentage of the WM area was significantly increased in the EO group compared to the NO group (P=0.008). However, there were no significant differences between the old rats trained with exercise and normal young rats (P ≥ 0.05).

The Number of Dark Cells

Nissl staining was used to visualize dark cells in the PFC (Figure 2A). The dark cells were shrunken neurons with an indeterminate nucleus around which vacuole areas may be seen.

As displayed in Figure 4B, the mean percentage of dark cells significantly increased in the NO group compared to the NY group (P < 0.001). Furthermore, the exercise could a significantly lower the percentage of dark cells of the PFC as observed in the EO group compared to the NO group (P < 0.001). There was no significant difference between other groups (P ≥ 0.05) **(Figure 2B)**.

The Percentage of MBP Intensity

The immunohistochemical assessment was carried out to determine the MBP intensity in the PFC (Figure 3A). A significant reduction was observed in the mean percentage of MBP intensity in the NO group compared to NY (P=0.009). In addition, the mean percentage of MBP positive area was significantly elevated in EO group compared to the control group (P=0.013). However, there were no significant differences between other groups (P ≥ 0.05) **(Figure 3B).**

Amount of Activity of GPx

As depicted in Figure 3A, there is a significant increase in the level of GPx activity in the NY group compared to NO group (P=0.011). Additionally, there was a higher GPx activity level in the EO group than the NO group (P=0. 037) **(Figure 4A)**. There was no significant difference between the EO and NY groups as well as in the NY and EY groups (P ≥ 0.05).

The Level of MDA

The mean MDA level significantly increased in the NO group compared to the NY group (P=0.004). A significantly increase of the mean MDA level was exhibited in the EO group compared to old rats without exercise (P=0.026) **(Figure 4B)**. No significant difference showed between the old rats trained with exercise and young rat without exercise (P ≥ 0.05).

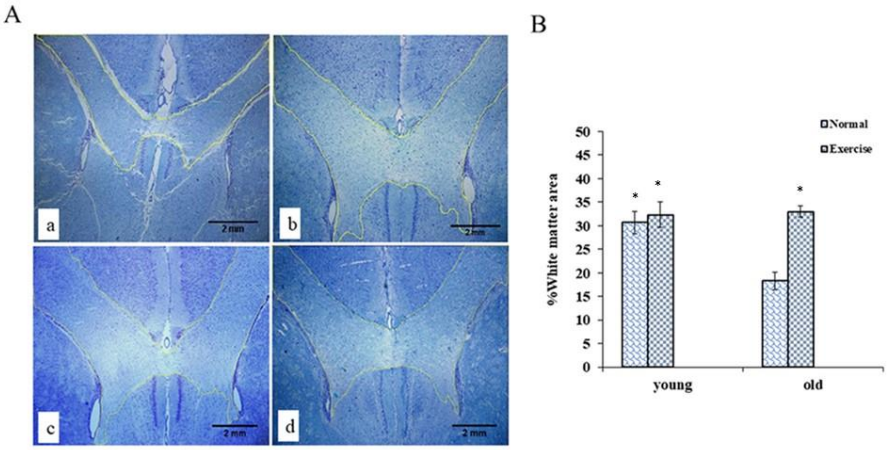

Figure 1. (A) Representative images of white matter erea following Toluidine blue staining ×40 (a–d); The NO group (a), EO group (b), NY group (c), EY group (d). (B) The comparison of the mean percentage of the WM area in different groups (* P < 0.05: significant difference between NY and NO group, # indicate significant difference at P < 0.05 between NO with EO group) (mean ± SEM).

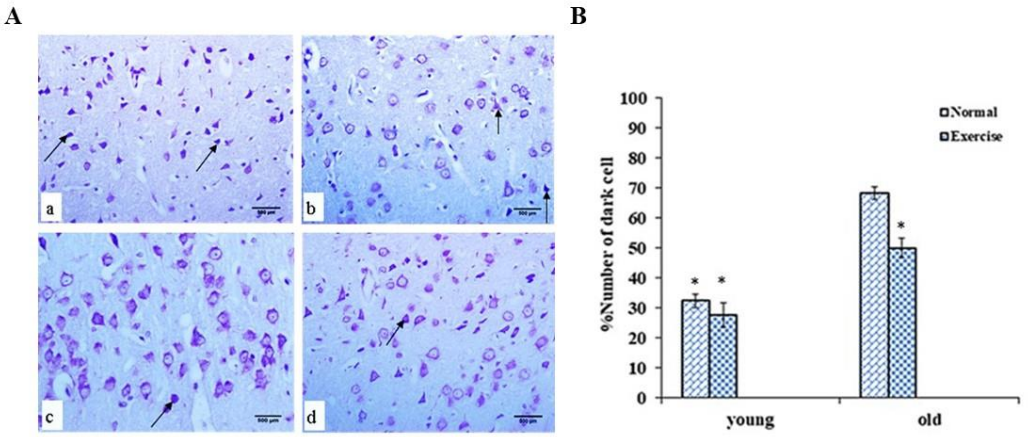

Figure 2. (A) Histology of PFC area for Cresyl-violet staining under light microscopy (a–d), The NO group (a), EO group (b), NY group (c), EY group (d) (× 400). (B) The comparison of the mean percentage of dark cells in the WM area in different groups (* P < 0.05: significant difference between NY and NO group, # indicate significant difference at P < 0.05 between NO with EO group) (mean ± SEM).

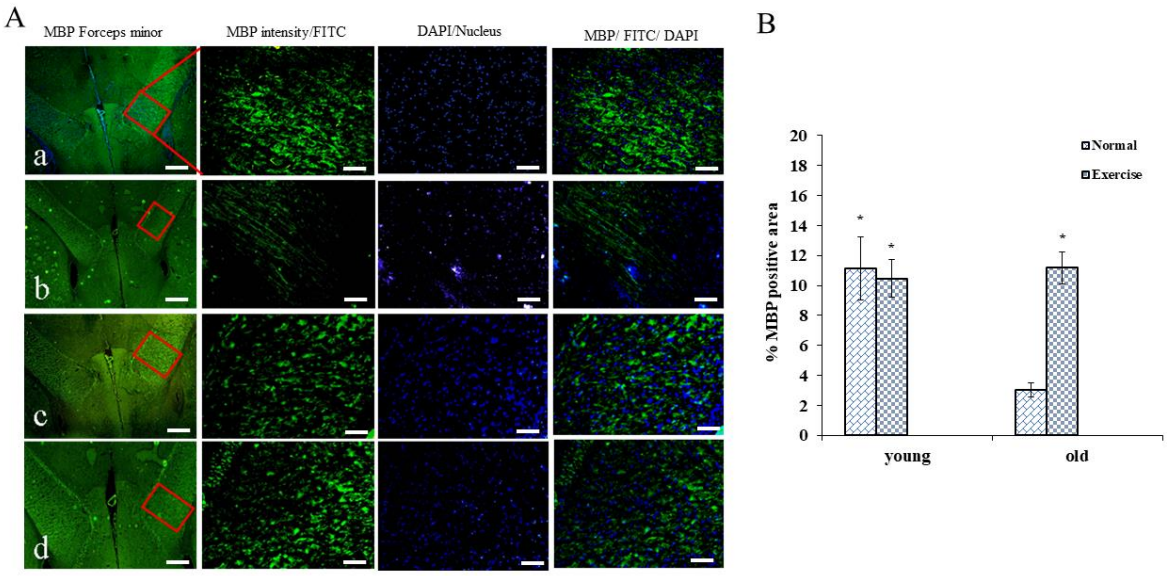

Figure 3. (A) The Immunohistochemistry photomicrograph of MBP Antibody and DAPI staining in different groups: NY group (a), NO group (b), EO group (c), EY group (d). (Scale bar is 200 µm for first column and 100 µm for other columns). The green show positively stained cells for MBP (green) and cell nuclei were labeled with DAPI (blue). (B) The comparison of the mean percentage of MBP positive cells in different groups (* P < 0.05: significant difference between NY and NO group, # indicate significant difference at P < 0.05 between NO with EO group) (mean ± SEM).

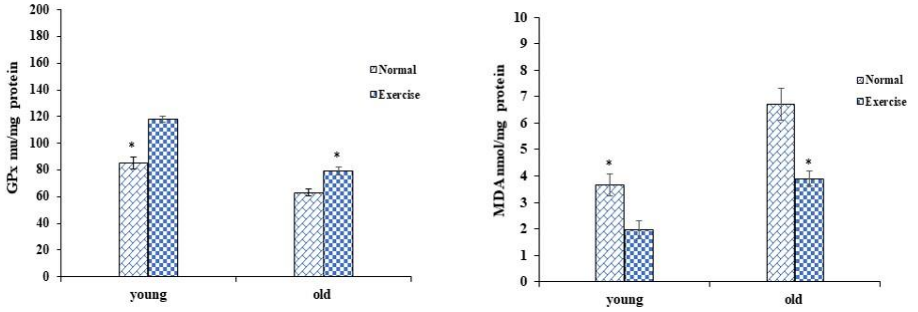

Figure 4. (A) The comparison of the mean level of glutathione peroxidase (GPx) in different groups, (B) The comparison of the mean level of malondialdehyde (MDA) (* P < 0.05 between NY and NO group, # P < 0.05 between NO with EO group) (mean ± SEM).

Discussion

The present study identified that the FAE program significantly enhanced the WM area of the PFC, GPx activity level, and MBP positive intensity. It also resulted in a significant reduction in the dark cell number of the PFC and MDA level in the EO group. Indeed, the exercise has deep effects on the biochemical environment which is related to the enhancement of neurotransmitters and growth factors **(25)**. The exercise boosts the blood circulation and improves the distribution of oxygen as well as nourishment to the brain **(26, 27)**. Also, secretion of various molecules such as BDNF **(28)**, serotonin, **(29)**, and insulin-like growth factor is enhanced during exercise. In addition, physical exercise stimulates the hypothalamic–pituitary–adrenal axis and elevates levels of circulating glucocorticoids **(30)**. Regular exercise has multiple beneficial effects including enhanced angiogenesis, diminished oxidative damage, increased activities of proteasome and neprilysin, reduced accumulation of carbonyls, and improved memory **(31).**

The present study found a significant reduction in the WM area of PFC in NO group. Also, we found that there were no significant differences in the mean of white matter area between the EO and NY.

WM pathways in the brain can be broadly classified into three primary groups: projection, commissural, and association tracts **(32).** According to a study, the diffusion properties in association WM tracts deteriorate to a greater extent than the commissural and projection fibers, so, the WM association tracts are more vulnerable during aging **(4)**. Also, many previous studies have shown a relatively progressive age-linked decline in the WM volume **(33, 34)**.In addition, our results showed a significant decline in MBP positive intensity for the NO group compared to the NY group. It has been proven that the myelin sheath progressively degrades and results in the loss of myelinated fibers of the nervous system in aging **(35)**. Indeed, reduction of axonal density and enhancement of axonal diameter are the main factors in age-associated WM deterioration **(36, 37)**; leading to reduced area of WM and the intensity of MBP (density of myelinated fibers) in aging, which was also observed in this study. Moreover, reduction of WM volume could be due to the loss of neurons along the aging process, which leads to the loss of nerve connections (axons and dendrites) **(38)**. Accordingly, we counted PFC dark neurons by Nissl staining which showed a significant increase in inactive or injured neurons in the NO group compared to the NY group.

The oxidative stress mainly increased during normal aging; this form of oxidative stress causes the denaturation of proteins, destruction of nucleic acids which may contribute to different neurodegenerative diseases in aging **(39)**. GPx is an oxidative enzyme to protect the organism against oxidative damage **(40)**. Evidence suggests that plasma antioxidant capacity

diminishes in the elderly due to a lowered level of GPx **(41)** that the our results are consistent with significant reduction of GPx activity level during aging without exercise.

Typically, MDA levels indicated oxidative damage, whereby lipid oxidation of cell membranes increases. After cell injury, a greater level of lipid oxidation can be observed in cell degeneration. During aging, high levels of MDA have also been reported **(42, 43)**; the results of the present study also confirmed that the aging process increases oxidative damage to cells and causes an increase in MDA as well as number of dark cells.

As mentioned above, the exercise protects against the degenerative aging process. We observed no significant difference between old exercise and normal young groups; probably, the FAE program would improve most normal aging defects such as the increase in WM volume, GP_X activity, and MBP positive intensity. Also, the present study demonstrated no significant difference between the normal young and the exercise young groups since the neurotransmitters, growth factors, BDNF, angiogenic proteins, antioxidant defense and blood supply naturally are at an optimum level in brain of young rats. This high level of factors prevent degenerative processes in the young brain.

Conclusion

The present study demonstrated that normal aging due to increased oxidative damage may have a deteriorating effect on the WM area, myelinated fiber, and antioxidant defense in the PFC area. According to our results, regular treadmill exercise appears to mitigate age-related degenerative process in the brain and delay the atrophy of white matter by protecting against myelinated fibers and reducing the number of dark cells in this area. Also, a reverse association was observed between the activity of GPx and levels of MDA and the protective effects of long-term exercise was proved on aged white matter. Thus, these findings imply that prolonged moderate and regular exercise may slow down the aging process in the brain.

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Authors' Contribution

SR conceptualized and designed the study. MEF and HR provided the data. EE, RS and SA conducted the statistical analysis and interpretation of the data. SR and MEF contributed to the writing and revision of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

This study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (Grant no. 393236).

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