Original Article

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Effect of Pioglitazone on Antioxidant Capacity and Oxidative Damage after Spinal Cord Injury in Rat

Z. Jahanbakhsh (MSc)[1], H. Ghoshooni (PhD)[1], M. Salehi (PhD)[2], M.T. Mohammadi (PhD)[*1, 2]

1.Department of Physiology and Biophysics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, I.R.Iran
2.Research Center of Neuroscience, Baqiyatallah University of Medical Sciences, Tehran, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Reduction of the antioxidant capacity and oxidative damage has a crucial role in development of damage after spinal cord injury. Since pioglitazone (PPAR-gamma agonist) have a powerful antioxidant property, the present study aimed to evaluate the effect of pioglitazone on antioxidant capacity and oxidative damage in the injured areas of spinal cord in rat.

METHODS: In the present experimental study eighteen male Wistar rats divided into three groups as follow (n=6); sham, control injured and pioglitazone-treated injured group. Spinal cord injury was performed according to the Ping-Weight Drop (contusion) model in rat. The animals received pioglitazone (3 mg/kg) intraperitoneally at times of 15 min after injury and then each 12 hours until a week. At the end, malondialdehyde level, activity of catalase and superoxide dismutase (SOD) enzymes and also histopathological alterations of spinal cord were assessed.

FINDINGS: Induction of spinal cord injury in control injured animals significantly increased the malondialdehyde levels (56%) and decreased the activity of catalase (48%) and SOD (65%) enzymes compared to sham group (P=0.004, P=0.001 and P=0.008, respectively). Pioglitazone in treated injured group significantly decreased the malondialdehyde levels (38%) and increased the activity of catalase (34%) enzyme compared to control injured group (P=0.038 and P=0.014, respectively). Also, pioglitazone prevented the histopathological changes of injured areas in spinal cord.

CONCLUSION: The findings of present study indicate that treatment with pioglitazone through potentiation of the antioxidant defense capacity of injured spinal cord decreases oxidative damage and also histopathological changes of spinal cord.

KEY WORD: *Spinal cord injury*, *Pioglitazone*, *Oxidative damage*, *Malondialdehyde*, *Antioxidant capacity*.

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*Corresponding Author: M.T. Mohammadi (PhD)
Address: Baqiyatallah University of Medical Sciences, South Sheikh Bahai St, Mullah Sadra Street, Tehran, I.R.Iran.
Tel: +98 21 82483419
E-mail: mohammadi.mohammadt@yahoo.com

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Introduction

Spinal cord injury (SCI) occurs with an annual incidence of 15-40% of every million worldwide (1). The incidence of complications from spinal cord injuries, such as motor defects is associated with the severity of primary mechanical damage and secondary pathophysiologic mechanisms after spinal cord injury (2,3). Primary mechanical damage initially causes necrosis, edema, hemorrhage, and vasospasm in the affected area (4). Then, some secondary pathophysiologic mechanisms are activated in this area that programmed cell death (apoptosis), inflammatory response, and the production of free radicals are one of the most important ones (2,5,6). Increasing the production and accumulation of reactive oxygen species (ROS) and ultimately the occurrence of oxidative stress is one of the most recognized mechanisms of post-traumatic spinal cord injury (2,7).

However, in normal conditions, the radicals and the oxidants produced in the nerve tissue are neutralized by the antioxidant defense system, but after spinal cord injury, the antioxidant capacity in the damaged area of the nerve tissue is weakened (8). An important part of the antioxidant defense system is formed of key enzymes such as superoxide dismutase and catalase, which in turn neutralize superoxide anions and hydrogen peroxide (9). In the injured areas of the spinal cord, the accumulation of free radicals is widespread, which is due to the weakening of the antioxidant defense, and partly due to the increase of the pro-oxidant enzymes (7,10). The accumulation of these free oxygen radicals damages the vital macromolecules of cells, such as proteins, membrane lipids, and nucleic acids (9). Therefore, the removal of these radicals in the affected regions of the spinal cord can greatly reduce the complications of spinal cord injury (11). PPeroxisome proliferator-activated receptor gamma (PPAR-gamma), such as pioglitazone delong to the family of Thiazolidinediones (TZDs). The use of these agonists activates various pathways of biological processes such as glucose metabolism, angiogenesis, lipidification and cell proliferation (12-14).

These drugs also have several other characteristics, including the anti-inflammatory nature, apoptotic inhibitors, anti-cancer and neuroprotective effects (12,15). The activation of PPAR-gamma prevents impaired nerve function after cerebral hemorrhage and inhibits inflammatory response with tissue damage (16). Previous research reported some of the antioxidant properties of these agonists in the pathological conditions of the nervous system, such as Parkinson's disease, Alzheimer's and stroke (18, 17,14). In a study, the effects of motor function improvement of pioglitazone have been reported in a spinal cord injury model (19). In research of Meng et al. Rosiglitazone had a better recovery effect on spinal cord injury than prednisolone (the only selective treatment for spinal cord injury) (12). The use of Rosiglitazone also increases the expression of the Brain Derived Neurotrophic Factor (BDNF) in spinal cord injury and reduces the expression of κB (NF-κB), a key factor in expression of many inflammatory factors (20).

The use of PPAR-gamma agonists also reduces the inflammatory factors such as TNF-α and IL-1β in spinal cord injured animals and in addition to decreasing the amount of myeloperoxidase enzymes, the motor symptoms have improved (19,12). Finally, the use of these agonists increases the proliferation of neural germ cells (12). Based on research conducted, PPAR-gamma agonists such as pioglitazone have a potent antioxidant nature. Therefore, due to the reduction of the antioxidant capacity of spinal cord injured tissue and the key role of oxidative damage in exacerbating spinal cord injury after spinal cord injury, the present study was conducted to evaluate the effect of pioglitazone on the amount of antioxidant capacity and oxidative damage in the lesion area of spinal cord in rat.

Methods

This experimental study after approval by the Ethics Committee of the Baqiyatallah University of Medical Sciences with registration code IR.BMSU.REC.1396.17 was performed on 18 male Wistar provided from the Laboratory Animal Research Center of Baqiyatallah University of Medical Sciences in the range of 200-250 gr. Animals were kept in standard conditions (12 hours of light and darkness at 22±2°C) without any restrictions of water and food. Lesion was created based on Ping-Weight Drop (contusion) model in rat (21). Animals were placed on a surgical table after anesthesia with isoflurane 2.5% (eruption, England) and the hair of the back area of the skin was shaved.

After disinfection of the target area, a longitudinal section along the vertebral column was made and loose tissues were removed and after removing paravertebral muscles and ligaments, laminectomy was performed on the animal's T-13 vertebrae. To create spinal cord injury, a designed device with 10 grams of weight was used at a height of 6 centimeters and a relatively severe

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lesion was caused in a specific area of the spinal cord. After the spinal cord injury, all cut pieces were sewn in two separate layers, and then the animal was kept in a proper place until complete vigilance was observed. At first, healthy rats were randomly divided into three groups: control, lesion control and treated group with pioglitazone. In the control animals, only laminectomy was performed. But the Ping-Weight Drop (contusion) model and spinal cord injury did not occur. In the lesion control group, spinal cord injury was performed by Ping-Weight Drop (contusion) model after surgery and spinal cord retrieval. In the pioglitazone-treated lesion group, the spinal cord injury was similar to that of the spinal cord injury control group, and the animals received pioglitazone (Avinash, India) at a dose of 3 mg/kg intraperitoneally at 15 minutes after spinal cord injury and then every 12 hours for one week. The choice of dosage, the method and duration of the injection are based on the previous studies (22,23). Meanwhile, the animals in the control and lesion control recieved DMSO intraperitoneally as pioglitazone solvent equivalent to animals treated with pioglitazone.

At the end of the experiment, the animals were placed under deep anesthesia and the spinal cord was removed completely in the T-12 to L-1 region. To evaluate the antioxidant system and pathologic features removed tissue was placed in liquid nitrogen and formalin 10%, respectively. The pathologic study was performed on the basis of the staining method of hematoxylin and eosin. The frozen tissues were also homogenized in 1:10 phosphate saline buffer, and then the samples were centrifuged at 14000 g and 4 ° C for 15 minutes. The supernatant was used to measure the level of malondialdehyde and to evaluate the activity of catalase and superoxide dismutase enzymes.

To determine the amount of malondialdehyde, 1.5 ml of Trichloroacetic Acid (TCA) 10% was added to 500 µl of homogeneous tissue and was centrifuged for 10 minutes, then 1.5 ml of the supernatant was removed and 2 ml of Thiobarbituric acid 0. 67% was added and was boiled for 30 minutes. Then 2 ml 1-butanol was added to the solution and, after severe vortex, centrifuged for 15 minutes at 4000 rpm. The absorbance of the supernatant solution was read at 532 nm. Finally, the amount of malondialdehyde was calculated in nanometers per milliliter (24). To measure the activity of the catalase enzyme, absolute ethanol (0.01 ml / ml) was added to a specific volume of tissue extract and incubated for 30 minutes. Then ten percent X-100 triton was added with a final concentration of one percent. This solution was used to measure enzyme activity. The reaction was started by adding 0.05 ml of H2O2 30 mM to the tissue sample in a potassium phosphate buffer of 50 mM pH =7. The absorbance was then read over 3-minute in wavelength of 240 nm. Enzyme activity was calculated based on unit per milliliter (25). To measure the activity of the superoxide dismutase enzyme, 0.2 ml 0.1 M EDTA in 0.3 mM Sodium cyanide, 0.1 ml of nitroblutterazolium (NBT) 1.5 mM and 200 µl of homogenized tissue (or buffer to control) were added to a cuvette and after mixing for 5 minutes was placed at 37 C. Then, 0.05 ml of Riboflavin 0.12 mM was added to potassium phosphate buffer 0.067, pH=7/8 and placed in room temperature for 12 minutes. The absorbance was then read over 5 minutes at 560 nm. Enzyme activity was calculated in units per milliliter (26). The results were analyzed using SPSS 21 software, ANOVA test and LSD post hoc test. $P<0.05$ was considered significant.

Results

Spinal cord injury significantly increased the level of malondialdehyde in spinal cord tissue 3.0±32.28 nmol/ml compared with the control group (1.44±0.31 nmol/ml) (p=0.004). While pioglitazone significantly decreased malondialdehyde of spinal cord in damaged areas in the treated group (2.06±0.44 nmol/ml) compared to the control group(p=0.035).

The level of catalase activity in the surgical site of the spinal cord in the control group was 2.0±68.15 units per milliliter (Fig 1).

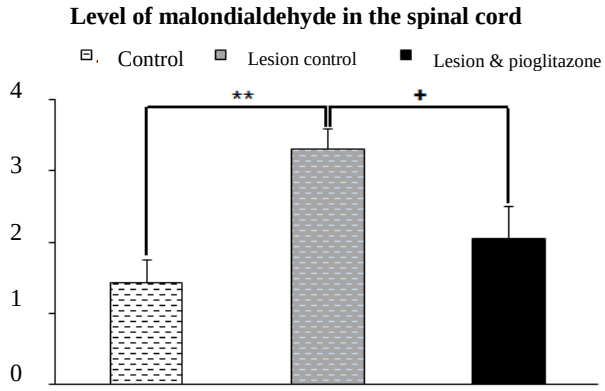

Figure 1. Effect of pioglitazone on malondialdehyde (nmol/ml) of spinal cord in the studied groups: Data are shown as SEM±Mean. ** indicates a significant difference with p = 0.004 in comparison with the control group. + indicates a significant difference with p = 035 compared with the control group.

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Spinal cord injury caused a significant reduction in catalase activity in spinal cord of animals in lesion control group (1.0±37.17 mg/dl) compared to control group (p=0.001). While the treatment with pioglitazone increased the activity of this enzyme in the injured spinal cord of animals in the treated lesion group compared to the control group (p=0.014), the numerical value of this group was 2.0±09.17 units per milliliter (Fig 2). The amount of superoxide dismutase enzyme activity in the spinal cord in animals in the control group was 1.13±0.13 units per milliliter (Fig 3). The formation of spinal cord injury significantly decreased the activity of this enzyme in animals in the control group of lesion (0.39±0.06 nmol/ml) compared to the control group (p=0.008). Pioglitazone increased the activity of the superoxide dismutase enzyme in the treated lesion group (0.76±0.2 nmol/ml) compared to the control group, but this increase was not statistically significant (p=0.135). Based on microscopic images of spinal cord tissue in the control group, spinal cord tissue and placement of neurons are normal. Neuronal damage as neurons with necrotized nuclei (dense and wrinkled nuclei) in the control group of the lesion is clearly visible. The rate of these changes in the spinal cord of animals in the group treated with pioglitazone is much lower than that of the lesion control group (Fig 4).

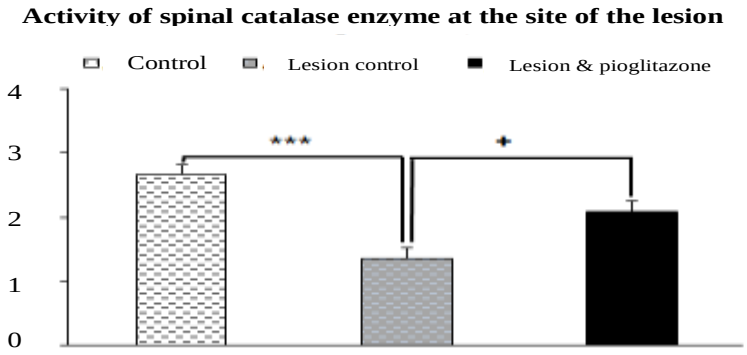

Figure 2. Effect of pioglitazone on the activity of catalase enzyme (units per milliliter) of spinal cord in the studied groups: Data are shown as SEM ± Mean. * indicates significant differences with p = 0.001 in comparison with the control group. + indicates a significant difference with p = 0.014 in comparison with the control group of the lesion**

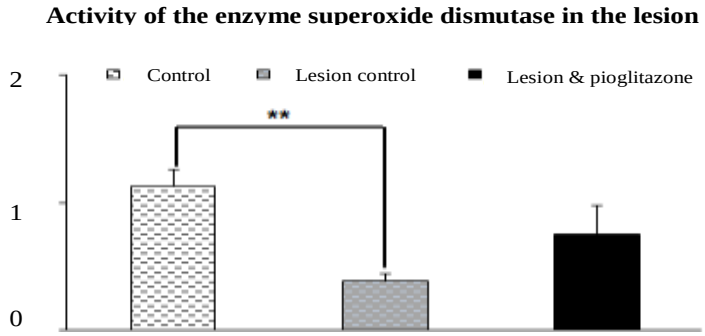

Figure 3. Effect of pioglitazone on superoxide dismutase enzyme activity (units per milliliter) of spinal cord in the studied groups: Data are shown as SEM ± Mean. ** indicates a significant difference with p = 0.008 in comparison with the normal group.

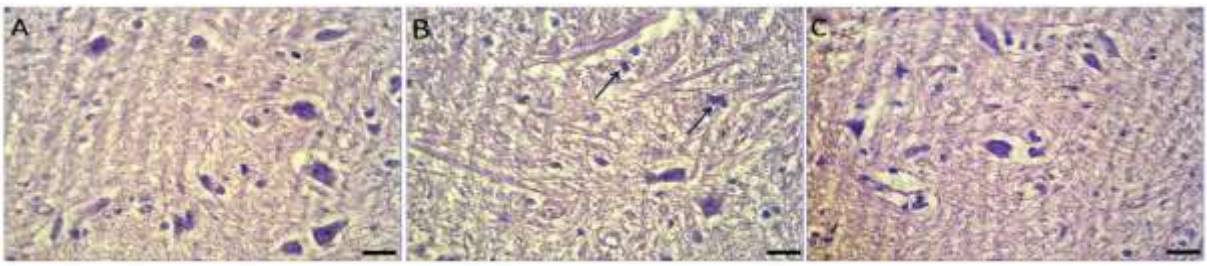

Figure 4. Images in areas of damaged spinal cord tissue stained with hematoxylin and eosin in control groups (A), control of the lesion (B) and the lesion treated with pioglitazone (C). In the control group of lesion, damaged spinal cord along with necrotized neurons are clearly observed (Scale bars: 20 µm, 400X).

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Discussion

Based on the findings of this study, the creation of spinal cord injury by Ping-Weight Drop (contusion) model led to oxidative damage and decreased antioxidant defense capacity of the spinal cord in the lesion area. While the treatment with pioglitazone significantly reduced the oxidative damage and histopathological chages of the spinal cord and improved the antioxidant defense capacity.

Accordingly, the reinforcement of the antioxidant defense system by pioglitazone can reduce the oxidative damage and the pathological changes caused by the spinal cord injury. Oxidative damage plays a key role in the development of primary lesion and secondary damage after injury to the spinal cord, leading to the spread of primary damage and exacerbation of the lesion (8, 7). The results of this study, as well as findings from previous studies demonstrated that after spinal cord injury, oxidative damage was observed in the injured area because malondialdehyde, an indicator of oxidative damage and peroxidation of lipids, increased significantly in this area.

Based on previous research, oxidative damage plays a major role in causing neuronal damage and damage to the nerve tissue (7), so that the histological results of the spinal cord in the injured area could indicate these injuries. After the spinal cord injury, the antioxidant defense system is significantly weakened (27, 8), which is well illustrated by the results of the present study. According to the results of this study, the reduction of superoxide dismutase enzyme activity results in the accumulation of superoxide anions in the lesion region. On the other hand, anion superoxide is compounded with nitric oxide, which is increased due to an increase in the induction of nitric oxide synthase enzyme and produces a toxic compound called Peroxy nitrate, which is highly toxic for neurons and nerve tissues (9). In addition, in the present study, the activity of catalase enzyme was significantly reduced in injured spinal cord. The inactivation of this enzyme results in the accumulation of hydrogen peroxide and then its decomposition into hydroxylation radicals, which are highly toxic and harmful for the DNA material (9).

Therefore, it can be concluded that reducing the antioxidant defense capacity has a fundamental role in causing oxidative damage in injured spinal cord. PPAR-gamma agonists such as pioglitazone have neuroprotective effects (17,15). Based on previous researches, the use of these agonists, which have an antioxidant nature, prevents damage to the nerve tissue (18). According to the results of this study, treatment with pioglitazone after spinal cord injury prevented the accumulation of free radicals and oxidative damage because pioglitazone reduced the amount of malondialdehyde in the damaged spinal cord. Due to the importance of oxidative damage in the exacerbation and expansion of spinal cord injury, pioglitazone reduces neuronal damage and nerve tissue damage in the lesion area by preventing oxidative damage.

Some of the antioxidant properties of pioglitazone are due to changes in the antioxidant capacity of the body tissues (28). According to the results of previous studies, the use of pioglitazone induced changes in the level of anti-oxidant enzymes such as glutathione peroxidase, catalase and superoxide dismutase in some pathological conditions (30, 29,18). In the present study, treatment with pioglitazone after spinal cord injury increased the activity of catalase enzyme in affected areas significantly more than control group of lesion . Moreover, the level of superoxide dismutase enzyme activity was higher in the treated lesion than in the control group of lesion. Similar to these results, the effects of potentiating the antioxidant defense capacity by pioglitazone have been reported in some pathological conditions such as ischemia and brain stroke (30, 29). On the other hand, since anti-oxidant enzymes are predominantly in peroxisomes, the use of PPAR-gamma agonists such as pioglitazone can effectively induce expression of these enzymes (6). Therefore, according to the results of this study and previous studies, pioglitazone could prevent from oxidative damage and histopathological changes of the injured spinal cord by increasing the antioxidant defense capacity and inhibiting the accumulation of free radicals . In addition, some other neuroprotective effects such as inhibition of apoptotic signals (15) and inhibition of inflammatory response (12), have been reported from PPAR-gamma agonists. According to the results of this study, the use of pioglitazone to strengthen the antioxidant defense capacity of the spinal cord prevents oxidative damage and pathologic changes during spinal cord injury. Accordingly, the use of pioglitazone after spinal cord injury may prevent secondary damage and spread of lesion and could be used as one of the treatment options to reduce the complications of spinal cord injury.

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