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Rosiglitazone protects the dorsal root ganglion cells and sciatic nerve after crush in rat

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Abstract

The aim of this study was to investigate the histological changes in the dorsal root ganglion (DRG) and the sciatic nerve in rats after sciatic nerve crush (SNC) and treatment with rosiglitazone. The rats were divided into four groups, each including seven animals, and underwent the following intervention. Group I: control animals which received carboxy methyl cellulose (0.5 w/v, p.o.). Group II: sham operated animals whose skin of the posterior thigh was opened, closed and the animals received the vehicle (carboxy methyl cellulose). Group III: SNC animals; the animals received the vehicle. Group IV: SNC with rosiglitazone (5 mg/kg body weight/day) dissolved in the vehicle. On the 28th day the fifth lumbar DRG and sciatic nerve were removed. Volume of the dorsal root ganglion, total volume and number of cells (A and B cells) of DRG, total surface area of the cells, and total number, diameter and cross-sectional area of the myelinated nerve fibres were estimated using stereological techniques. No change was observed in volume of the DRG, but all of the other parameters were decreased after nerve crush. In SNC+ rosiglitazone treated rats, the parameters decreased but to a lesser extent in comparison with the non-treated SNC group.
It can be concluded that rosiglitazone has a protective effect on the DRG cells and sciatic nerve after crush in rats.

Key words: *rosiglitazone, dorsal root ganglion, sciatic nerve, stereology.*

Introduction

Sciatic nerve crush is commonly experienced in pregnancy, gunshot trauma and systemic disease such as diabetes. These types of nerve injuries cause loss of sensory, motor and autonomic functions [12]. The sciatic nerve is the largest nerve in the body and the peripheral nervous system and extends from the hip to the sole of the foot. Sciatic nerve crush (SNC) induces inflammatory and oxidative responses, and apoptosis of the cells of the dorsal root ganglion (DRG) [17]. After SNC, Wallerian degeneration arises around the region of the lesion [22,3]. Some anti-inflammatory and neuroprotective drugs have been tried to reduce the inflammation of the injured nerve, ganglions, spinal cord injury, and Alzheimer's and Parkinson's diseases [19].

Rosiglitazone is a peroxisome proliferator-activated receptor gamma (PPARγ) and appears to have an anti-inflammatory effect in addition to its effect on

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insulin [6]. The goal of this study was to investigate the effects of rosiglitazone on the cells of the DRG and sciatic nerve (number, area and diameter of fibre) after sciatic nerve crush using stereological techniques. The volume of the ganglion, mean A and B cell volume, total volume and surface area of the A and B cells were investigated in the DRG of SNC and SNC+ rosiglitazone treated rats. In addition the total number, diameter and the area of the myelinated nerve fibres in proximal and distal segments of the nerve were estimated in the above-mentioned animals.

Material and methods

Ethics

All the animals were selected from the laboratory animal centre of Shiraz University of Medical Science and were approved by the animal ethics committee of the university by agreement No. 89-5123.

Animals and treatments

Twenty-eight adult female Sprague-Dawley rats weighing 200-220 g were used in this study. Animals were divided into four groups of seven rats. In the first group, control rats received daily orally doses of the vehicle (carboxy methyl cellulose). In the second group, sham operated rats whose skin and fascia of the posterior thigh were opened and closed, the rats received daily orally doses of the vehicle. In the third group, the sciatic nerve was injured, and the animals were treated with the vehicle. In the fourth group, the sciatic nerve was crushed and the animals were treated with rosiglitazone (5 mg/kg body weight/day) dissolved in carboxy methyl cellulose [13]. All the medications were administered beginning on the 1st day after the crush and continued until the 28th day [17]. All animals were kept in a laboratory with standard conditions at the temperature of 22-24°C and also received food and water freely.

Surgical procedure

The animals underwent surgery after anaesthesia with ketamine (60 mg/kg body weight) and xylazine (8 mg/kg body weight). Before surgery the skin of the right hind limb was shaved and sterilized with povidone-iodine solution. Through an approximately 1.5 cm incision on the posterior of the thigh, the right sciatic nerve was crushed in the third and fourth groups. Sciatic nerves were pressed for 30 s by haemostat forceps. In the sham-operated animals the sciatic nerve was not subjected to crush. At the end of surgery the fascia and the skin were sutured with 3-0 nylon thread. For prophylaxis of infection topical oxytetracyclin spray was used for 7 days after surgery [1,17].

Tissue preparation

On the 28th day after sciatic nerve injury, all the animals were anesthetized with ether overdose. The animals were perfused transcardially with normal saline and buffered formaldehyde. The fifth lumbar dorsal root ganglion (DRG) and the proximal and distal segments of the sciatic nerve were removed and fixed in buffered formaldehyde for 48 hours. For estimating some of the stereological parameters of the ganglion, isotropic uniform random sections (IUR) are

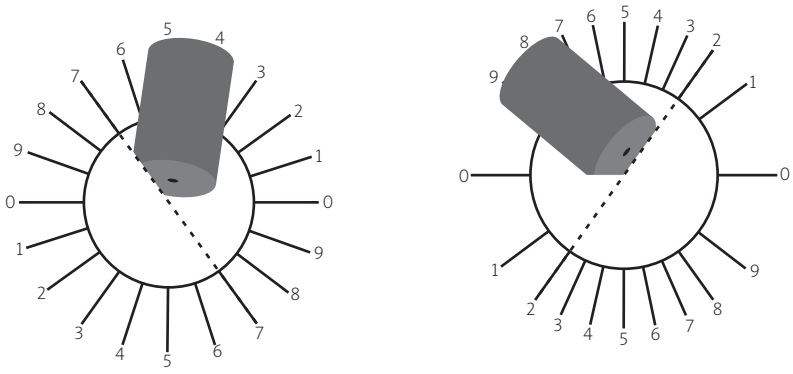


Fig. 1. DRG was embedded in a cylindrical block and placed on the φ-clock. A random number (here 7) was selected and the block was cut in the selected directions without damage to the DRG. The block was placed on the θ-clock and a new number (here 2) was selected and the block was cut in that direction again. The DRG was sectioned executively in the second direction using a microtome.

necessary. The orientator method was applied to obtain the IUR sections [9]. A brief explanation of the method is given under Fig. 1. The DRG was sectioned executively with a microtome (thickness: 25 μm). The proximal and distal segments of the nerve were sectioned (thickness: 4 μm). To prevent over-projection due to thickening of the sections of the DRG, all estimations were done using a 60X lens with NA = 1.4. The maximal focus plane was considered for this study. The sections were mounted on slides and stained with Heidenhain's Azan stain [14]. All examinations were done using a Nikon (E-200) microscope linked to a computer.

Stereological study

Estimation of the volume of the ganglion

Cavalieri's method was applied to estimate the volume or size of the ganglion using the following formula:

$$V_{reference} = \Sigma P_i \cdot T \cdot a/p,$$

where $V_{reference}$ is volume of the ganglion, ΣP_i is the total number of the points hitting the compartment in the selected sections, T is the distance between the sections, (a/p) is the area per point (here 0.045 mm^2) [2].

Estimation of the number-weighted mean cell volume

To estimate the volume of A and B cells, the nucleator method was applied. In this method the cells are sampled according to their number (disector principle), using an electronic microcator (MT12, Heidenhain, Germany) in thick sections. Briefly, the cells which were selected by the optical disector were considered for estimation of the volume. The distance from the centre of the selected nucleolus to the border of the cytoplasm (l_n) [10,18] was measured (Fig. 2). The following formula was used for estimation of cell volume (V_N):

$$V_N = \frac{4\pi}{3} l_n^3$$

Estimation of total volume of A and B cells

Volume density of the cells was estimated using:

$$Vv = \Sigma P\,[A \text{ or } B] / \Sigma P\,[total]$$

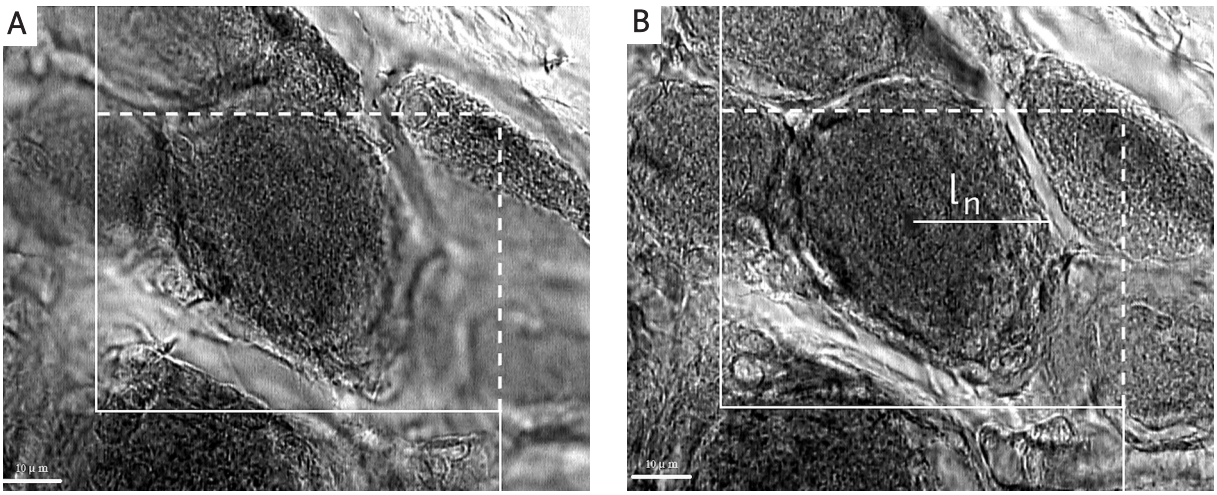


Fig. 2. Estimation of the cell volume using a nucleator. The unbiased counting frame was superimposed on the images to sample the cells using the dissector principle. Only the cells whose nucleoli were not visible at the initial dissector height (**A**) and were visible at the following optical scan (**B**) were sampled. Only the cells whose nucleoli were completely or partly inside the counting frame or touching the upper and right lines were sampled. The distance from the centre of the selected nucleolus to the border of the cytoplasm was measured and cell volume was estimated using: $V_N = \frac{4\pi}{3} l_n^3$

The absolute total volume of A and B cells was obtained by multiplying density by the total volume of the dorsal root ganglion:

$$V = Vv \times V_{reference}$$

where ΣP *[A or B]* indicates the number of points hitting the cells and ΣP *[total]* is the number of points hitting the reference space (Fig. 3) [4].

Estimation of total surface area of A and B cells

The cell surface density was estimated using the following formula:

$$Sv = \frac{2I}{\Sigma P \times \frac{l}{p}}$$

The absolute total surface area of the A and B cells was obtained by multiplying the density by the total volume of the dorsal root ganglion:

$$S = Sv \times V_{reference}$$

I shows the number of intersections between the cell surface and test lines, *l/p* is the length of the test line per point, and *P* is the number of points superimposed on the reference space (Fig. 3) [4].

Total number of A and B cells

The total volume of A or B cells was divided by each mean cell volume obtained using the nucleator method to estimate the mean number of cells.

Estimation of the total number of myelinated nerve fibres

The total number of myelinated nerve fibres was estimated with the fractionator method. Two dial gauges were used to show the movement of the microscope stage in x and y directions. An unbiased counting frame was superimposed on the sciatic nerve cross-section [7]. About 200-300 profiles were counted per nerve segment by the following formula (Fig. 4):

$$N = \frac{1}{sf} \times Q$$

$$sf = \frac{a\ (frame)}{a\ (sample)}$$

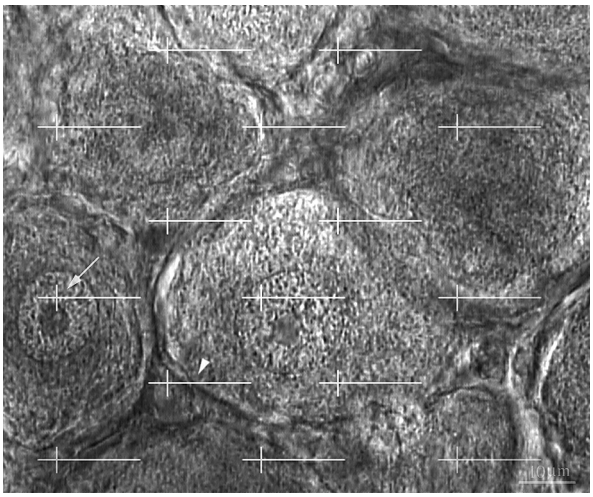


Fig. 3. To estimate the volume and surface density of A and B cells, a grid of points and lines was superimposed on the images of the sections. Volume density was estimated by dividing the total number of points (the arrow) hitting the cells by the total number of points hitting the reference area. Surface density was estimated using:

$$Sv = \frac{2I}{\Sigma P \times \frac{l}{p}}$$

where "*I*" is the intersection of test lines with the cell border (the arrow head), "*l/p*" is the length of test line per point, and "*P*" is the number of points (the arrow) superimposed on the reference space.

where *sf* is the sample fraction, *a* (*frame*) is the area per frame (here it was 128 μm^2), *a* (*sample*) is the sampling area (here it was 2500 μm^2), and *Q* is the number of myelinated nerve fibres.

Estimation of the myelinated nerve fibre diameter and area

The diameter of the myelinated nerve fibre was estimated on the myelinated nerve fibre sampled by the counting frame. The broadest line that was running approximately through the central point of the nerve fibre and also was vertical to the longest axis of the nerve fibre was considered as the diameter. The 2D-nucleator method was used to estimate the cross-sectional areas of the myelinated fibres [7]. From the approximate central point of the nerve fibre, the length of the two test lines (perpendicular to each

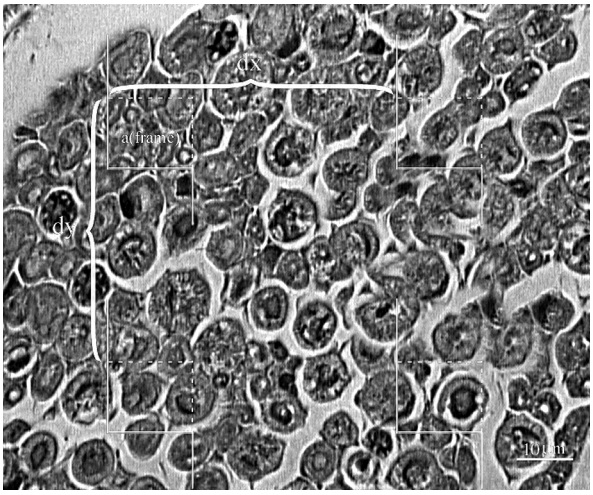


Fig. 4. Estimation of the total number of myelinated nerve fibres, using the fractionator method. The unbiased counting frame with "$a_{(frame)}$" was superimposed on the images. "$a_{(sample)}$" was dx × dy. The first counting frame was placed randomly. The selecting frame was systematically displaced in the "dx" or "dy" direction equally in a systematic uniform random method using the dial gauges attached to the microscope stage. The total number of myelinated nerve fibres was obtained by the product of nerve fibre profile counted in the determined fraction and the inverse sampling fraction.

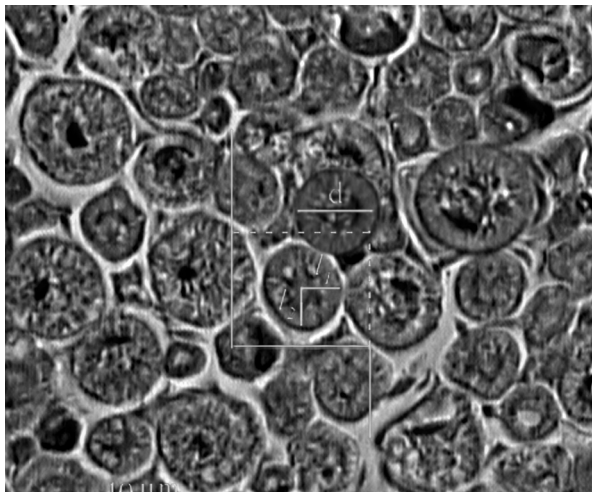


Fig. 5. Estimation of the diameter and area of the myelinated nerve fibre. The broadest line that was running approximately through the central point of the nerve fibre and also was vertical to the longest axis of the nerve fibre was considered as the diameter "d". To estimate cross-sectional area of the myelinated fibre with the 2D-nucleator method, the length of two test lines from the approximate central point of the nerve fibre to the nerve fibre boundary, *l*, was measured and the area was estimated using the following formula: $a = \pi \, l_i^2$.

other) from the centre to the nerve fibre boundary, *l*, was measured (Fig. 5). The area was estimated using the following formula:

$$a = \pi l_i^2$$

Statistical analysis

All data were analysed by application of Mann-Whitney and Kruskal-Wallis tests. *P*-values less than 0.05 were considered as significant. Mean ± standard deviation and total observation variation (CV = SD/mean) were reported.

Results

Volume of the ganglion

The mean volume of the ganglion did not show any differences between the control group and other groups (Table I, Plot 1).

Volume of the A and B cells

The mean volume of A and B cells was reduced by ~37% and ~43% in the sciatic nerve crushed group in comparison with the sham-operated rats ($p < 0.002$). In the rats with injured sciatic nerve treated with rosiglitazone, the volume of A and B cells was decreased to a lesser extent than in the SNC group. This means that in SNC+ rosiglitazone treated rats, the volume of A and B cells was ~31% and ~47% higher than in the non-treated SNC rats ($P < 0.002$) (Table II).

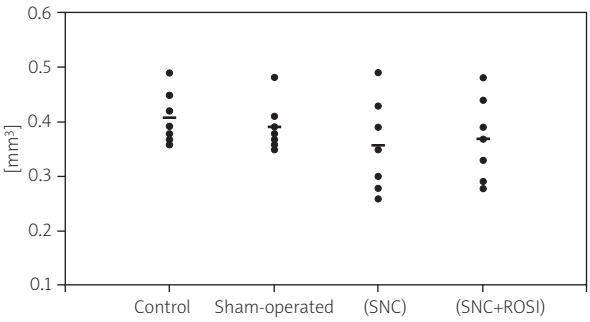
Total volume of A and B cells

The total volume of A and B cells was reduced by ~58% and ~55% in the sciatic nerve injured rats in comparison with the sham-operated group ($p < 0.002$). In the SNC+ rosiglitazone rats, the total volume of A and B cells was decreased to a lesser extent than in the SNC group. This means that in SNC+ rosiglitazone

Table I. Mean ± standard deviation and total observed variation (CV) of the volume (mm^3) of the dorsal root ganglion, total volume (mm^3) and total surface area (mm^2) of A and B cells in the control, sham-operated, and sciatic nerve crush (SNC) with or without rosiglitazone (ROSI) treatment

Groups	Parameters									
	Total volume						Total surface area			
	Ganglion	CV	A cell	CV	B cell	CV	A cell	CV	B cell	CV
Control	0.40 ± 0.05	0.12	0.293 ± 0.018	0.06	0.089 ± 0.009	0.10	38.4 ± 4.17	0.10	25.2. ± 1.82	0.07
Sham-operated	0.36 ± 0.06	0.16	0.292 ± 0.015	0.05	0.090 ± 0.006	0.06	40.2 ± 3.01	0.07	25.5 ± 2.10	0.08
SNC	0.35 ± 0.08	0.22	0.103 ± 0.022*	0.21	0.029 ± 0.01*	0.34	15.0 ± 4.7*	0.31	13.07 ± 1.91*	0.14
SNC+ROSI	0.36 ± 0.07	0.19	0.188 ± 0.034*	0.18	0.056 ± 0.006*	0.10	22.9 ± 5.5*	0.24	16.42 ± 1.42*	0.08

$p<0.002$ (SNC) vs. (Sham-operated) and (SNC+ROSI) vs. (SNC)



Plot 1. Absolute volume of the ganglion in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.

Table II. Mean ± standard deviation and total observed variation (CV) of the volume of A and B cells of the dorsal root ganglion in the control, sham-operated, and sciatic nerve crush (SNC) with or without rosiglitazone (ROSI) treatment

Groups	Volume			
	A cell	CV	B cell	CV
Control	42 932 ± 1534	0.03	7689 ± 477	0.06
Sham-operated	27 007 ± 1362*	0.03	7614 ± 583	0.07
SNC	35 528 ± 4230*	0.05	4268 ± 940*	0.22
SNC+ROSI	35 528 ± 4230*	0.11	6300 ± 525*	0.08

$p < 0.002$ (SNC) vs. (Sham-operated) and (SNC+ROSI) vs. (SNC)

treated animals the total volume of A and B cells was ~41% and ~25% higher than in the non-treated SNC rats ($P < 0.006$) (Table I, Plots 2 and 3).

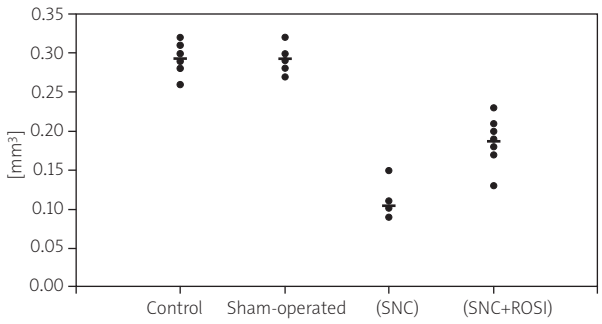
Total surface area of A and B cells

The data revealed that the mean total surface area of A and B cells was reduced by ~62% and ~48% in the SNC as compared with the sham-operated animals ($p < 0.002$). In the rats with SNC+ rosiglitazone, the absolute surface area of A and B cells was decreased to a lesser extent than the SNC. That is, in the SNC+ rosiglitazone treated animals, the surface area of A and B cells was ~52% and ~26% higher than the non-treated injured rats ($P < 0.002$) (Table I, Plots 4 and 5).

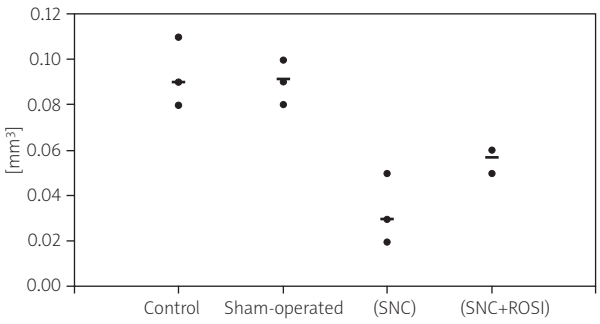
Table III. Mean ± standard deviation and total observed variation (CV) of the number of A cells and B cells of the dorsal root ganglion in the control, sham-operated, and sciatic nerve crush (SNC) with or without rosiglitazone (ROSI) treatment

Groups	Parameter			
	Number			
	A cell	CV	B cell	CV
Control	6860 ± 279	0.04	11597 ± 766	0.06
Sham-operated	6821 ± 348	0.05	11841 ± 648	0.05
SNC	3781 ± 567*	0.14	6576 ± 685*	0.10
SNC+ROSI	5231 ± 442*	0.08	8974 ± 392*	0.04

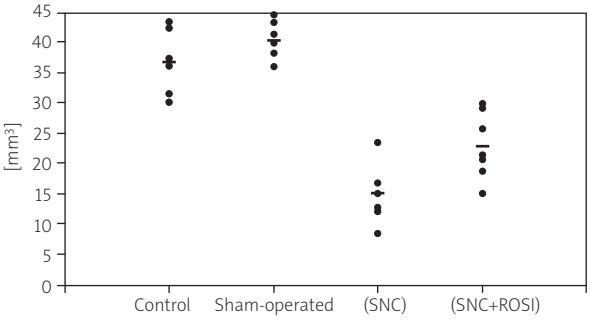
$p < 0.002$ (SNC) vs. (Sham-operated) and (SNC+ROSI) vs. (SNC)



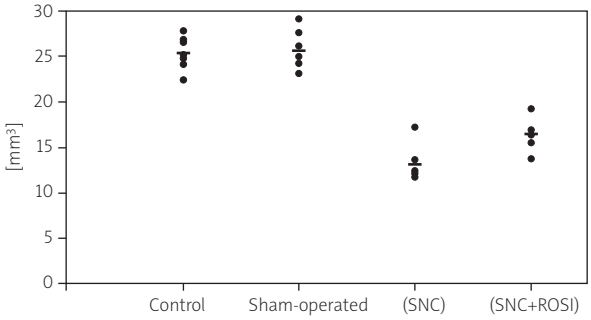
Plot 2. Total volume of A-cells in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.



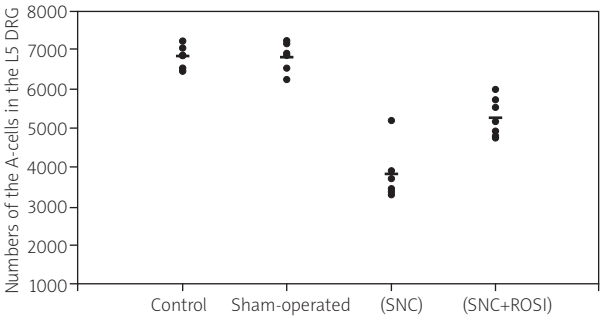
Plot 3. Total volume of B-cells in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.



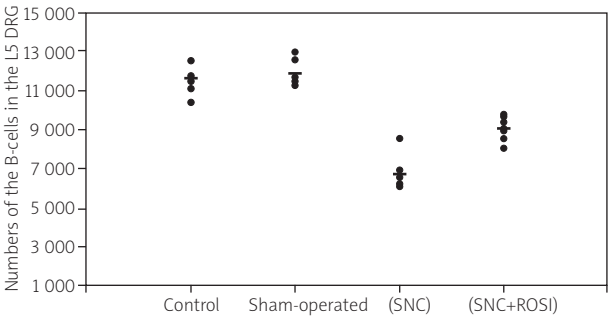
Plot 4. Total surface of A-cells in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.



Plot 5. Total surface of B-cells in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.



Plot 6. Total number of the A-cells in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.

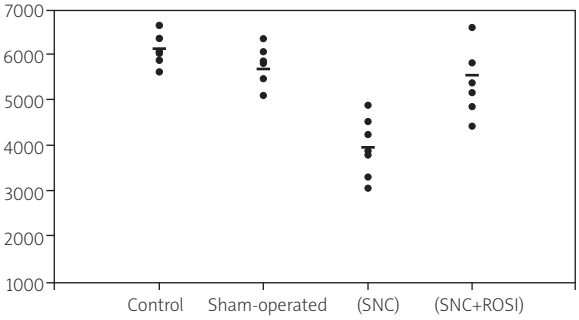


Plot 7. Total number of the B-cells in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.

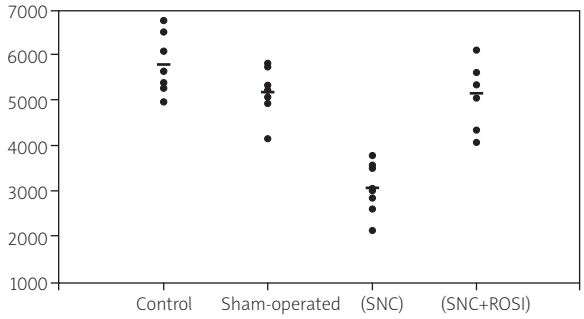
Table IV. Mean ± standard deviation and total observed variation (CV) of the number, diameter (µm) and area (µm²) of myelinated nerve fibres of the proximal and distal segments in the control, sham-operated, and sciatic nerve crush (SNC) with or without rosiglitazone (ROSI) treatment

Groups	Parameters											
	Number				Diameter				Area			
	Proximal	CV	Distal	CV	Proximal	CV	Distal	CV	Proximal	CV	Distal	CV
Control	6134 ± 334	0.05	5802 ± 663	0.11	5.7 ± 0.4	0.07	5.4 ± 0.4	0.07	32.8 ± 2.08	0.06	30.57 ± 1.8	0.05
Sham-operated	5677 ± 472	0.08	5191 ± 547	0.10	5.8 ± 0.6	0.10	5.3 ± 0.5	0.09	31.9 ± 2.1	0.06	31.01 ± 0.9	0.02
SNC	3954 ± 644*	0.16	3082 ± 585*	0.18	3.9 ± 0.5*	0.12	3.7 ± 0.5*	0.13	21.3 ± 3.6*	0.16	18.3 ± 2.9*	0.15
SNC+ROS	5542 ± 834*	0.15	5168 ± 727*	0.14	5.3 ± 0.6*	0.11	5.2 ± 0.8*	0.15	29.7 ± 1.9*	0.06	26.6 ± 2.9*	0.10

**p < 0.006 (SNC) vs. (Sham-operated) and (SNC+ROSI) vs. (SNC)*



Plot 8. Total number of the myelinated nerve fiebers of the proximal segment in control, sham-operaed, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.



Plot 9. Total number of the myelinated nerve fiebers of the distal segment in control, sham-operated, sciatic nerve crush (SNC), with or without rosiglitazone (ROSI) treatment rats.

Total number of A and B cells

The data revealed that the mean total number of A and B cells was reduced by ~80% in the SNC as compared with the sham-operated animals ($p < 0.002$). In the rats with SNC+ rosiglitazone, the total number of A and B cells was decreased to a lesser extent than in the SNC rats. That is, in the SNC+ rosiglitazone treated animals, the number of A and B cells was ~38% and ~36% higher than in the non-treated injured rats ($P < 0.002$) (Table III, Plots 6 and 7).

Total number of myelinated nerve fibres

The data revealed that the mean total number of myelinated nerve fibres of the proximal and distal segments was reduced by ~31% and ~41% in the SNC in comparison with the sham-operated animals ($p < 0.006$). In the sciatic nerve crushed rats treated with rosiglitazone, the total number of myelinated nerve axons was decreased to a lesser extent than in the sham-operated group. After treatment of SNC animals with rosiglitazone, the total number of myelinated nerve fibres was ~40% and ~67% higher than in the non-treated SNC rats ($P < 0.002$) (Table IV, Plots 8 and 9).

Diameter of myelinated nerve fibres

The mean diameter of the myelinated nerve fibres of the proximal and distal segments was reduced by ~33% and ~30% in the SNC in comparison with the sham-operated group ($p < 0.002$). In the rats with SNC+ rosiglitazone, the diameter of the myelinated nerve fibres of the proximal and distal segments was decreased to a lesser extent than in the SNC rats.

After treatment of SNC with rosiglitazone, the diameters of the myelinated nerve fibres of the proximal and distal segments were ~37% and ~41% higher in comparison with the non-treated injured rats ($P < 0.006$) (Table IV).

Area of myelinated nerve fibres

The area of myelinated nerve fibres of the proximal and distal segments was reduced by ~33% and ~41% in the SNC in comparison with the sham-operated group ($p < 0.002$). In the sciatic nerve crushed rats treated with rosiglitazone, the area of the myelinated nerve fibres of the proximal and distal segments was decreased to a lesser extent than in the SNC rats. After treatment of SNC with rosiglitazone the area of the myelinated nerve fibres of the proximal and distal segments was ~39% and ~44% higher than in the non-treated injured rats ($P < 0.006$) (Table IV).

Discussion

The present study was designed to evaluate the effects of rosiglitazone on the histological parameters of the dorsal root ganglion and sciatic nerve after SNC. The fifth lumbar DRG sends the most numerous fibres into the sciatic nerve and this nerve in rat is a suitable model for functional recovery assessment. SNC causes intensive changes in the DRG including reduction of the number of cells [11]. In the present study structure of the DRG and sciatic nerve were assessed using stereological methods [11]. Previous studies show the histological changes following sciatic nerve crush. It has been reported that the ganglion volume was reduced after sciatic nerve crush [11]. This was not accordance with our results, in which we observed that the volume of the ganglia was not different following crush injury. Using stereological methods it is possible to estimate the volume of individual perikarya. It has been indicated that there was a reduction in mean perikaryon volume following sciatic nerve crush [19]. In that research the total volume and surface area of the A and B cells after sciatic nerve crush were not reported. We reported previously that after nerve crush, the numerical density of A and B cells was decreased considerably using the optical dissector method [14]. In the present study the number of cells was estimated in an indirect method as described in the materials and methods section. There was no difference in the cell numbers between the two methods of estimation. Previous studies have reported loss of cells [3,11,15]. Reduction in volume of A and B cells, and shrinkage of A and B cells have been reported after SNC [11,19]. These findings are in accordance with the present evaluation. It has been shown that the number-weighted mean volume of A and B cells was reduced following sciatic nerve crush [3,11,15,19] and this claim was in accordance with our present results, in which we found that the mean cell volume and total cell volume were decreased following the injury. The cell surface is an important structure due to its communication with outer and inner cell environments. In the DRG the cell surface is also a place of interaction with supporting satellite cells. Therefore quantitative estimation of this parameter can show us measurable structural changes of the cell wall. Reduction of this parameter has not received attention in most nerve injury evaluation. The parameter is presented here.

A previous study reported morphological changes such as decrease in the number and size of myelinated nerve fibres after sciatic nerve injury [22]. Our results are in accordance with those findings. We found that the total number, diameter and area of the myelinated nerve fibres were decreased.

One of the main goals of this study was to investigate whether administration of rosiglitazone influenced the histology of the dorsal root ganglion and sciatic nerve in rats subjected to sciatic nerve crush. Our stereological study showed the protective effects of rosiglitazone. Reduction of all of the above-mentioned parameters was ameliorated using rosiglitazone. After SNC, inflammatory mediators such as bradykinin, prostaglandin, TNF-α and interleukin-1 β were increased and cyclo-oxygenase-2 (COX-2) upregulated around the site of injury [8]. Rosiglitazone was the subject of this survey because it has received a lot of attention recently. Rosiglitazone has been used as a neuro-protective compound in central nervous system complications such as experimental Alzheimer's disease [20]. In addition rosiglitazone has shown its ameliorative potential in peripheral nervous system diseases such as tibial and sural nerve transection-induced painful neuropathy in rats [5]. Rosiglitazone as a PPARγ agonist reduced astrogliosis, microglia activation, myelin loss and neuropathic pain, and ameliorated motor function recovery after spinal cord injury [16]. Rosiglitazone is a member of the thiazolidinedione class of drugs. Thiazolidinediones act as insulin sensitizers and are used for the management

of type II diabetes mellitus and reducing blood glucose. Rosiglitazone appears to have an anti-inflammatory effect in addition to its effect on insulin resistance. Rosiglitazone is a nuclear factor kappa-B (NF-kB) inhibitor which down-regulates the inflammatory pathways. When rosiglitazone is administered, NF-kB levels decrease [6].

Conclusion: Rosiglitazone has a neuroprotective effect on the dorsal root ganglion and sciatic nerve structure after sciatic nerve crush in rats.

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