Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2020; 27 (4): 338-347

Effect of Troxerutin on Oxidative Stress Induced by Sciatic Nerve Ischemia-reperfusion Injury in Rats

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Received: 16 June, 2019 Accepted: 11 August, 2020

ARTICLE INFO

Article type:
Original Article

Keywords:
Troxerutin
Sciatic Nerve
Ischemia-Reperfusion
Rat

Abstract

Background: Troxerutin has antioxidant and anti-inflammatory properties and in this study, its antioxidant effect on the reduction of oxidative stress induced by ischemia-reperfusion sciatic nerve injury was investigated.

Methods: In this study, 64 male rats were randomly divided into 8 groups as follows: 1- IR2: ischemia (3 hours) and reperfusion (2 days), 2- Trox+IR2: ischemia (3 hours) and reperfusion (2 days), 3- IR7: ischemia (3 hours) and reperfusion (7 days), 4- Trox+IR7: ischemia (3 hours) and reperfusion (7 days), 5- IR14: ischemia (3 hours) and reperfusion (14 days), 6- Trox+IR14: ischemia (3 hours) and reperfusion (14 days), 7- IR28: ischemia (3 hours) and reperfusion (28 days), 8- Trox+IR28: ischemia (3 hours) and reperfusion (28 days). The rats received 150 mg/kg troxerutin in one injection (single dose). After separation of serum, biochemical parameters of the serums such as NO, PON1, CAT, and GPX were measured.

Results: Troxerutin significantly increased the GPX and PON1 levels in groups that their reperfusion time was 2 and 14 days ($P<0.05$). There was no significant difference in the levels of NO and CAT between the groups received troxerutin and control groups ($P>0.05$).

Conclusion: Troxerutin relatively decreased the oxidative stress in the sciatic nerve ischemia-reperfusion injury by increasing the level of antioxidant enzymes.

Citation: Dadpisheh S, Ahmadvand H, Jafaripour L, Nouryazdan N, Babaeenezhad E, Shati H, Bagheri SH. Effect of Troxerutin on Oxidative Stress Induced by Sciatic Nerve Ischemia-reperfusion Injury in Rats. Journal of Kerman University of Medical Sciences, 2020; 27 (4): 338-347.

Introduction

Ischemia can lead to pathological changes and neuropathic disorders in the peripheral nerves, especially in the sciatic nerve. The anaerobic respiration not only decreases free radicals in tissue but also increases the rate of free radicals production. Reperfusion, as a secondary injury, induces the production of oxygen free radicals, hydroxyl radicals, and other oxidative products that attack the tissue and cause cell destruction greater than ischemia (1-3). In normal conditions, there is a balance between the production and elimination of free radicals. The disequilibrium in these processes leads to oxidative stress and cell destruction. Oxidative and non-oxidative enzymes are the body's major defense systems against injury induced by free radicals (4). As antioxidants can destroy toxic oxygen metabolites, they can also play an important role in resisting against ischemia/reperfusion injuries (5). Troxerutin, a trihydroxyethylated derivative of the natural bioflavonoid rutin, is found in tea, vegetables, and fruits. Troxerutin has antithrombotic, antifibrinolytic, antioxidant, and anti-inflammatory properties, therefore, it can be used in the treatment of vascular problems, diabetes, and cancer; it also has protective effects on nerve cells (6,7). In addition, it can destroy free radicals (8). Hence, the present study was conducted to investigate the impacts of this antioxidant in reducing oxidative stress induced by ischemia/reperfusion sciatic nerve injury through evaluating the levels of catalase (CAT), paraoxonase 1 (PON1), glutathione peroxidase (GPX), and nitric oxide (NO).

Materials and Methods

Animals

In this study, 64 Sprague-Dawley rat (weighting 250-300 g) were selected and kept at a temperature of 22˚C and humidity of 45-46% under a 12-h light/dark cycle in the animal lab of Lorestan University of Medical Sciences for one week. The studies were conducted in groups at the same intervals.

Experimental groups and drug treatment

Rats were randomly divided into 8 groups as follows: 1) IR2: Sciatic nerve ischemia for 3 hours + reperfusion for 2 days + injection of normal saline, 2) Trox+IR2: Sciatic nerve ischemia for 3 hours + reperfusion for 2 days + injection of 150 mg/kg troxerutin, 3) IR7: Sciatic nerve ischemia for 3 hours + reperfusion for 7 days + injection of normal saline, 4) Trox+IR7: Sciatic nerve ischemia for 3 hours + reperfusion for 3 days + injection of 150 mg/kg troxerutin, 5) IR14: Sciatic nerve ischemia for 3 hours + reperfusion for 14 days + injection of normal saline, 6) Trox+IR14: Sciatic nerve ischemia for 3 hours + reperfusion for 14 days + injection of 150 mg/kg troxerutin, 7) IR28: Sciatic nerve ischemia for 3 hours + reperfusion for 28 days+ injection of normal saline, 8) Trox+IR28: Sciatic nerve ischemia for 3 hours + reperfusion for 28 days + injection of 150 mg/kg troxerutin.

At the early phase of reperfusion, both normal saline and troxerutin were injected intraperitoneally.

Surgical procedure

Rats were intraperitoneally anesthetized by injection of ketamine (50 mg/kg) and xylazine (5 mg/kg) (9). Then, the animals were placed in the supine position and their sciatic nerve ischemia was dissected using Saray method. In this manner, after identification of inguinal region, a section was made there and the femoral nerve was cut from the femoral vein and artery (10) and the artery and vein were occluded by silk cotton (6/0) using Split-Knot technique for 3 hours (11), then,

they were opened and reperfusion was induced. After reperfusion, the blood samples were taken from animals and centrifuged at 3000 rpm for 15 minutes. Finally, the serum levels of parameters such as GPX, CAT, NO, and PON1 were measured.

Measurement of glutathione peroxidase (GPX)

Glutathione peroxidase was evaluated according to the method of Rotruck et al. (12). As completely described in our previous study (13), a mixture of hydrogen peroxide (H_2O_2), tert-butyl hydroperoxide (TBHP) with serum samples was used, and then, the absorption of samples was read using ELISA reader tool at 420 nm.

Measurement of catalase

Catalase was measured according to the method of Aebi (14), which was fully described in our previous study (15), and briefly described as follows: 0.7 ml phosphate buffer (pH=7.4) and 0.10 ml hydrogen peroxide (H_2O_2) were mixed with 100 ul of serum samples, then, the decrease of absorption was read by a spectrophotometer at 240 nm in 30 seconds for 3 minutes.

Measurement of paraoxonase 1 (PON1)

Paraoxonase was assessed according to the method of Blatter et al. (16). Paraoxon was used as a substance. The activity of this enzyme was evaluated at 25˚C, then, the increase of its absorption was read using a spectrophotometer at 412 nm.

Measurement of nitric oxide

Nitric oxide was assessed according to the method of Griess et al. (17). For this purpose, 50 ml of Griess solution (1% sulfanilamide in 2.5% phosphoric acid solution) was added to 100 ml of serum samples. After 10 minutes, another solution (50 ul N-naphthyl-ethylenediamine, ul phosphoric 0.1% acid) was added. Then, its absorption was read by the ELISA reader at 560 nm.

Ethical issues

The protocols of the study were approved by the Animal Ethics Committee of Lorestan University of Medical Sciences. Also, they were in accordance with the guidelines of the National Health Institute (NIH1978) and Medical Research Council. Additionally, all of our experimental procedures and stages of the assessments were performed in conformity with the Research Ethics Committee of the University and Iranian Ethical Guidelines for the Application of Animals in Research. (Code: 1860).

Statistical analysis

The findings were analyzed using Mann-Whitney U test and SPSS version 21. Statistical significant level was considered at $P<0.05$. Data were expressed as mean ± standard deviation (mean ± SD).

Results

The effect of troxerutin on serum GPX level in ischemia/reperfusion injury of animals' sciatic nerve

The comparison of plasma activity of GPX between case (received troxerutin) and control (did not receive troxerutin) groups showed a significant increase in the group received troxerutin, after reperfusion for 2 days ($P<0.05$) (Figure 1).

There was no significant difference in the plasma density of GPX between case and control groups after 7 days of reperfusion ($P>0.05$) (Figure 1).

Troxerutin could increase the plasma activity of GPX in case group after 14 days of reperfusion compared to the control group (P<0.05) (Figure 1).

There was no significant difference in the plasma density of GPX between case and control groups after 28 days of reperfusion (P>0.05) (Figure 1).

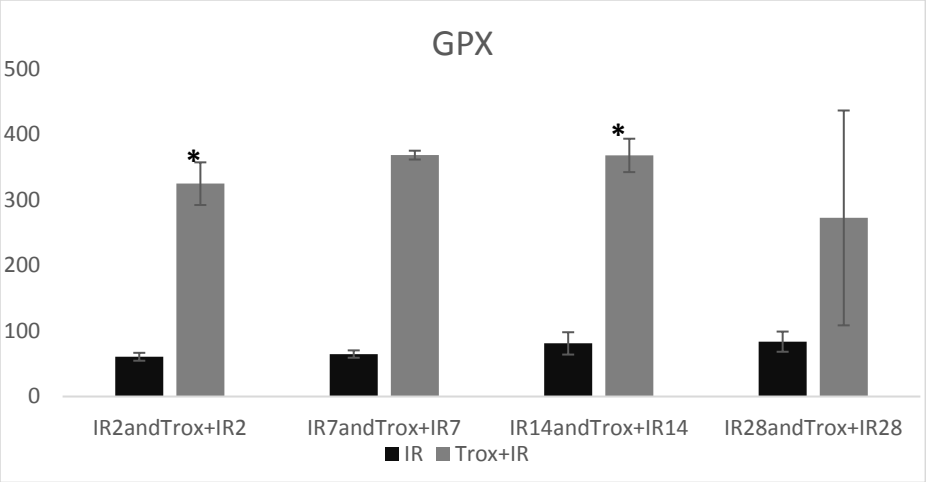

Figure 1. Effect of troxerutin on sciatic nerve ischemia/reperfusion injury in plasma GPX. Data were expressed as mean ± SD (n=8). Data were analyzed by the Mann–Whitney U test. Differences were considered statistically significant when P<0.05.

The effect of troxerutin on serum CAT level in ischemia/reperfusion of animals' sciatic nerve

There was no significant difference in the serum CAT level in group treated with troxerutin after the 2nd, 14th, 28 th days of reperfusion (P>0.05) (Figure 2). But its level in the group treated with troxerutin after 7 days of reperfusion indicated a significant difference (P<0.05).

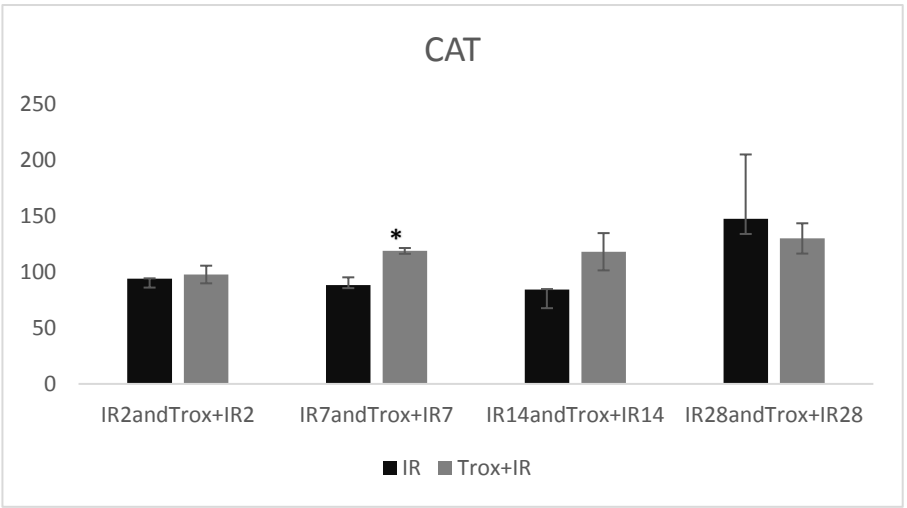

Figure 2. Effect of troxerutin on sciatic nerve ischemia/reperfusion injury in plasma CAT. Data were expressed as mean ± SD (n=8). Data were analyzed by the Mann–Whitney U test. Differences were considered statistically significant when P<0.05.

The effect of troxerutin on serum PON1 level in ischemia/reperfusion of animals' sciatic nerve

There was a significant difference in the plasma density of PON1 between the case and control groups after 2 days of reperfusion (P<0.05) (Figure 3).

The plasma density of PON1 between the group received troxerutin (Trox+IR7) and the group did not receive troxerutin after the 7th day of reperfusion (IR7) was not significantly different (P>0.05) (Figure 3).

The plasma density of PON1 in the group received troxerutin (Trox+IR14) and the group did not receive troxerutin after the 14th day of reperfusion (IR14) was not significantly different (P>0.05) (Figure 3).

The plasma density of PON1 in the group received troxerutin significantly increased after the 28th day of reperfusion compared with that did not receive troxerutin (P<0.05) (Figure 3).

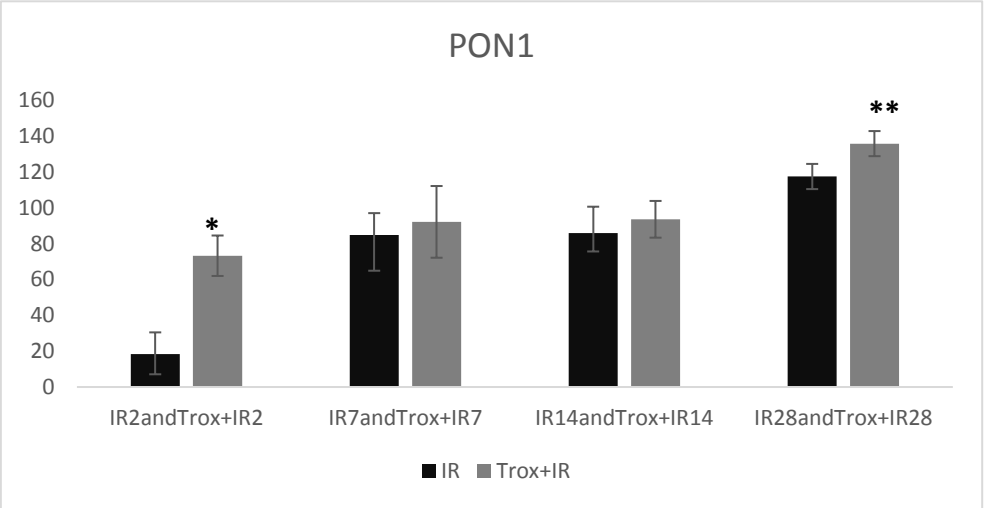

Figure 3. Effect of troxerutin on sciatic nerve ischemia/reperfusion injury in plasma PON1. Data were expressed as mean ± SD (n=8). Data were analyzed by the Mann–Whitney U test. Differences were considered statistically significant when P<0.05.

The effect of troxerutin on serum NO level in ischemia/reperfusion of animals' sciatic nerve

The comparison of NO level between case and control groups indicated that serum NO level in the group treated with troxerutin showed no significant difference compared with that was not treated with troxerutin (P>0.05) (Figure 4).

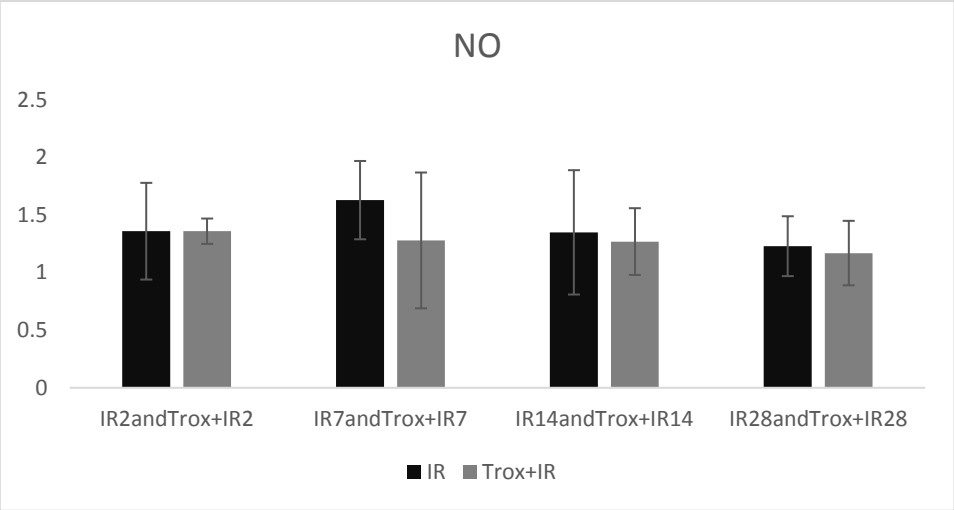

Figure 4. Effect of troxerutin on sciatic nerve ischemia/reperfusion injury in plasma NO. Data were expressed as mean ± SD (n=8). Data were analyzed by the Mann–Whitney U test. Differences were not significant statistically (P>0.05).

Discussion

In the present study, after 3 hours of sciatic nerve ischemia, reperfusion was conducted in different groups at different time intervals (2, 7, 14, and 28 days), and injection of a single dose 150 mg/kg troxerutin led to improves the activity of antioxidant enzymes such as GPX, CAT and PON1. The animals were anesthetized by injection of ketamine (50 mg/kg) and Xylazine (5 mg/kg) and the blood samples were taken. Their serum was used to assess parameters such as GPX, CAT, NO, and PON1.

As axons are more resistant to ischemia, they experienced little injury compared with perikaryon. Ischemia-reperfusion of axons of peripheral nerves causes inflammation and edema at the site of injury, and as a result, causes serious disorder in the nerve structure and function (18). Partial sciatic nerve ligation (PSNL) leads to the release of toxic materials from neutrophils and macrophages that causes inflammation and production of reactive oxygen species (ROS) (19). NO acts as an oxidant, so the sciatic nerve injuries induce an increase in the NO level followed by neuropathic pain (20-22). According to previous studies, antioxidants such as quercetin (23), syringic acid (18), liquiritin (24), azadirachta indica (25), and aloe vera (26) decrease oxidative stress and neuropathic pain and improve histopathological changes induced by sciatic nerve ischemia/reperfusion injury due to their antioxidant and anti-inflammatory properties. Troxerutin improves diabetic cardiomyopathy in diabetic rats through decreasing oxidative stress and suppressing ROS and NF-KB (26), and prevent cardiovascular diseases with its anti-inflammatory and anti-arrhythmic properties (27). The increased levels of antioxidant enzymes after receiving troxerutin in patients with type 1 diabetes indicates antioxidant activity (28). Antioxidant and metal-chelating properties of troxerutin cause a nephroprotective effect according to the nickel toxicity model (29). In addition, troxerutin causes a reduction in oxidative stress and dyslipidemia-induced hypertension in animal models (30). Furthermore, it improves metabolic syndrome by decreasing oxidative stress, increasing antioxidant capacity, decreasing insulin resistance, and improving serum biochemical parameters such as blood glucose, cholesterol, and triglyceride (31). A study by Kandhare et al. (2017) indicated

that the level of NO can be decreased by azadirachta indica, thus, inhibiting oxidative stress of sciatic nerve (22). In the present study, it was found that 150 mg/kg troxerutin reduced NO level over the days of reperfusion, although this decline was not significant. However, in this study, the injection was given only a day, which can be the reason for the low level of NO reduction in different groups. The level of CAT in groups that received troxerutin increased, but compared with group of troxerutin + IR7, this increase was not significant. The level of GPX in the two groups of troxerutin + IR2 and troxerutin + IR14 was significantly increased but in the other two groups, the increase was not significant. Paraoxonase 1, as an antioxidant and anti-inflammatory enzyme, causes lipid peroxidation and decreases oxidative stress (32). In the present study, troxerutin increased the PON1 level, but this increase in groups that had 2 and 28 days of reperfusion, was significant. However, the increase of serum antioxidant level may be due to the antioxidant property of troxerutin. Some studies have reported a significant increase in all of the oxidative enzymes and a decrease in oxidative stress following the use of troxerutin, may be due to its use for a longer period compared with the present study (28,31). Some studies showed that injection of 150 and 300 mg/kg/day troxerutin for 4 and 2 weeks reduced ROS and oxidative stress, respectively (26,33). On the other hand, the effect of troxerutin on NAFLD/NASH progression to hepatocarcinogenesis with three doses of 12.5, 25, and 50 mg/kg during 16 weeks was exanimated by Thomas et al. (34). They found that the lowest dose of troxerutin (12.5 mg/kg) was not observed to be effective, which might be due to insufficient concentrations to counter the adverse effects of hepatocarcinogenesis. Although, the highest dose (50 mg/kg) showed beneficial effects, the medium dose (25 mg/kg) was identified as an effective optimum dose for hepatocarcinogenesis (34). In recent studies, troxerutin increased the activity of GPX, CAT, SOD, and GSH, and decreased the activity of MPO, MDA, and ROS (26,28,29,33,34), which is consistent with the results of this study indicating the anti- effects of troxerutin on oxidative stress. In the present study, if troxerutin had been used as a pretreatment and for a longer period, better results might have been obtained.

Conclusion

According to the results, receiving a single dose of troxerutin (150 mg/kg) in the sciatic nerve ischemia/reperfusion injury model increased the levels of serum antioxidants such as GPX, CAT, PON1, and decreased NO. There was a slight reduction in oxidative stress but this reduction was not very effective. The use of this drug as a pre-treatment or for a longer period may be more effective in reducing oxidative stress. However, further studies on this issue are needed.

Acknowledgments

The study was conducted in accordance with the ethical principles of Research Ethics Committee of the University and Iranian Ethical Guidelines. The authors would like to sincerely thank laboratory staffs, Razi Herbal Medicines Research Center, and Lorestan University of Medical Sciences for their cooperation and financial support.

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