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Research Article

Dimethyl Fumarate Attenuates Kidney Ischemic Reperfusion Injury via Inflammatory and Oxidant Pathways

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Abstract

Purpose: Ischemia-reperfusion (IR) is one of the major causes of acute kidney injuries (AKI) as well as kidney transplant failure. Its underlying mechanisms include inflammatory, oxidant, and apoptotic pathways which result in nephron dysfunction. Dimethyl fumarate (DMF), is an immunomodulatory drug mostly used in multiple sclerosis, psoriasis, and auto-immune diseases. Regarding its anti-inflammatory and anti-oxidant history, this study aimed to investigate the effect of DMF on kidney IR by evaluating inflammatory and oxidant pathways.

Methods: The IR was induced by clamping the kidneys for 30 minutes. DMF was gavaged in 5, 15 and 45 mg/kg doses for 4 days pre-IR. The samples were collected on the 5th day of the experiment. Blood urea nitrogen (BUN) and creatinine were measured as markers of kidney function. Tumor necrosis factor (TNF-α) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) levels were measured by enzyme-linked immunosorbent assay (ELISA) kits and Superoxide dismutase (SOD) and Glutathione S-transferase (GSH) levels were evaluated by pyrogallol and Ellman assays respectively.

Results: The 45 mg/kg dose of DMF was excluded from the study due to toxic effects. DMF (15 mg/kg) decreased the IR-induced BUN and creatinine as well as TNF-α and NF-κB levels. The SOD and GSH levels which were elevated in IR groups were reduced by DMF (15 mg/kg) administration.

Conclusion: It can be suggested that DMF attenuates IR development through anti-inflammatory and anti-oxidant pathways.

Keywords: Dimethyl Fumarate; Ischemia-reperfusion; Kidney; Nephroprotective

Abbreviations

AKI: Acute Kidney Injuries; ANOVA: One-way Analysis of Variance; BUN: Blood Urea Nitrogen; DMF: Dimethyl Fumarate; DMSO: Dimethyl Sulfoxide; ELISA: Enzyme-linked Immunosorbent Assay; ERK: Extracellular Signal-regulated Kinase; GSH: Glutathione S-transferase; IL-1β: Interleukin 1 Beta; IL-6: Interleukin-6; IR: Ischemia Reperfusion; MS: Multiple Sclerosis Disease; NF-κB: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; NIS: National Institutes of Health Guide; NOS: Reactive Nitrogen Species; Nrf-2: Nuclear Respiratory Factor-2; ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase; TNF-α: Tumor necrosis factor;

Introduction

Renal Ischemic-reperfusion (IR) involves a phase of reduced oxygen supply to the tissue which is followed by the phase of blood flow back after a while. It usually results in acute kidney injury (AKI), which has a high mortality rate besides being accompanied by diseases such as lupus nephritis, crushes injury, sepsis, and dehydration [1,2]. Although the AKI mortality rate and hospitalization cost have been enhanced recently, to the best knowledge of the researcher any useful drug has not been reported for decreasing the deterioration of this situation [2]. On the other hand, kidney transplant which is the last treatment choice for end-stage renal diseases is strongly limited due to IR-induced graft rejection [3].

Despite the known harmful effects of IR, the prevention of this phenomenon is of concern nowadays. Recently, the involvement of inflammatory pathways such as neutrophil and macrophage migration and stimulated production of pro-inflammatory factors like Interleukin 1 beta(IL-1β), Interleukin-6 (IL-6), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Tumor necrosis factor (TNF-α) has been suggested in renal IR [4,5].

Also, it has been reported that during the kidney injury and lack of blood supply, free radicals including reactive nitrogen and oxygen species (NOS and ROS) are produced in cell mitochondria by NADPH oxidase and nitric oxide synthase which lead to the impairments of essential biomolecules (RNA and DNA) [6,7].

Taken together, these factors alter the activity of the vascular and hemodynamic systems of the kidney, glomerular filtration, and the mechanism of reabsorption and secretion in different parts of the nephron. Finally, apoptosis, necrosis, and changes in gene expression occur in renal cells [8,9].

Dimethyl fumarate (DMF) belongs to a group of drugs called Nuclear respiratory factor-2 (Nrf2) activators. Many studies have been done on this drug concluding DMF is the second line of the oral treatment for severe psoriasis [10].

Regarding its anti-inflammatory and immune system modulatory effects, it is also widely used for multiple sclerosis disease (MS). Nowadays, in addition to the proven uses against MS and psoriasis, the drug is also used in Sarcoidosis, Alopecia, Chronic Uveitis, and Cheilitis [11,12]. Its mechanism of action is known as inhibiting leukocytes' function and altering cytokine expression [13]. In addition, DMF inhibits inflammation by reducing the NF-κB and TNF-α levels in the body [14]. Besides having anti-inflammatory effects, this drug has exerted anti-oxidant effects by acting on myelinoaxons and increasing the expression of Nrf2 factors in astrocytes which results in induced tissue survival [15]. Regarding the anti-inflammatory and anti-oxidant effects of DMF and the role of inflammation and oxidant pathways in IR damage, in this study, we intended to investigate the protective effects of DMF on renal IR.

Materials and Methods

Animals

30 Wistar male rats weighing 200-250 g were purchased from the Faculty of Pharmacology, University of Tehran. The rats were housed under standard conditions including 12 h light/dark and a temperature of 20-23 °C. All experiments were performed by the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH Publications No. 80-23). Rats were randomly divided into 5 groups consisting of 6 rats: 1. Control, 2. Sham, 3. 5 mg/kg DMF, 4. 15 mg/kg DMF and 5. 45 mg/kg DMF.

DMF administration

DMF (1408024.0393 Cinnagen) solution was prepared every day freshly. The drug was dissolved in normal saline and dimethyl sulfoxide (10% DMSO) and was orally gavaged based on the weight of rats through intragastric gavage [16]. The experiment lasted 5 consecutive days. For the first 3 days, the drug was gavaged twice a day in rats for 4 hours. On the 4th day, 30 minutes before the anesthesia, another dose of the drug was given to the rats and then ischemia was induced. On the 5th day, the blood was collected from the animal's heart and was centrifuged for further analysis of serum blood urea nitrogen (BUN), creatinine, TNF-α, NF-κB, and Superoxide dismutase (SOD), and Glutathione S-transferase (GSH) levels [17].

Surgical procedure

For inducing IR, the animals were first anesthetized by intraperitoneal injection of a mixture of ketamine (80 mg/kg) and xylazine 10 mg/kg under sterile conditions. After induction of the anesthesia, a midline incision was made and pulled over the viscera. The left and right kidneys were occluded by a microvascular clamp to achieve kidney ischemia. To ensure the correct induction of ischemia, the color of the kidneys was checked to be reduced within a few seconds after placing the clamps. After 30 minutes of clamping, the blood flow was returned to the kidneys.

Biomarker analysis

To calculate the amount of SOD, the Tris-HCL and Pyrogallol solution was used and the level of SOD was measured at 420 nm by a Spectrophotometer [18]. Also, the amount of GSH was measured by the Ellman assay. Due to this method, the total and free sulfhydryl groups were measured in biological samples [19]. Moreover, for the determination of TNF-α and NF-kB levels, the rat TNF-α enzyme-linked immunosorbent assay (ELISA) Kit (ab46070) and rat (NFKB) ELISA Kit (LS-F37358) were used respectively.

Statistical analysis

Comparative analysis was conducted by one-way Analysis of variance (ANOVA) followed by the post hoc Tukey's test and $p<0.05$ was considered significant. The data were analyzed using the statistical software GraphPad Prism 8.

Result

Evaluation of serum creatinine

During the study, it was observed that the 45 mg/kg dose of DMF not only did not improve kidney function but also it raised the level of serum creatinine and BUN. As a result, this dose of DMF was removed from further experiments.

The serum creatinine level evaluation showed an increase of it in the ischemic group compared to the sham group. However, in the group receiving the dose of 15 mg/kg of DMF, a significant decrease in creatinine was observed (Figure 1).

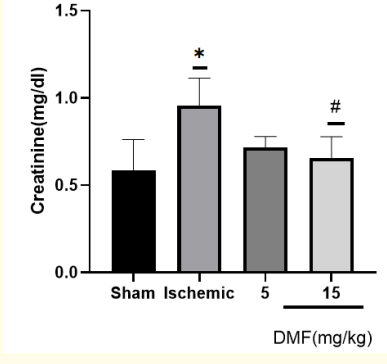

Figure 1: The effect of DMF on serum creatinine in kidney ischemia-reperfusion. Serum creatinine increased in the ischemic group (*P < 0.05 compared to the sham group). The level of serum creatinine decreased in DMF 15 mg/kg group (#P < 0.05 compared to the ischemic group). Data are presented as Mean ± SEM, (N = 6).

Evaluation of BUN level

Regarding the BUN measurement results, a significant increase in BUN level occurred in the ischemic group compared to the sham group. Also, in the DMF 5 mg/kg and 15 mg/kg groups a significant reduction of BUN was observed (Figure 2).

Figure 2: The effect of DMF on BUN level in kidney ischemia-reperfusion. The BUN level increased in the ischemic group (***P < 0.001 compared to the sham group). The level of BUN decreased in DMF 5 mg/kg and 15 mg/kg groups. (### P < 0.001 compared to ischemic group). Data are presented as Mean ± SEM, (N = 6).

Evaluation of SOD and GSH level

SOD and GSH level measurements showed that the ischemic group had significantly lower SOD and GSH levels. However, both SOD and GSH levels increased significantly in DMF 15 mg/kg group in comparison with the ischemic group (Figure 3 and Figure 4).

Figure 3: The effect of DMF on SOD level in kidney ischemia-reperfusion. The SOD level decreased in the ischemic group (** P < 0.01 compared to the sham group) and increased in DMF 15 mg/kg group significantly (# P < 0.05 compared to the ischemic group). Data are presented as Mean ± SEM, (N = 6).

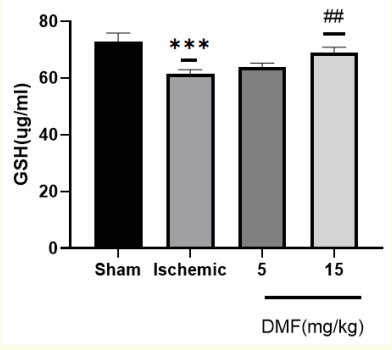

Figure 4: The effect of DMF on GSH level in kidney ischemia-reperfusion. The GSH level declined in the ischemic group (*** P < 0.001 compared to the sham group) and raised in DMF 15 mg/kg group significantly (## P < 0.01 compared to the ischemic group). Data are presented as Mean ± SEM, (N = 6).

Evaluation of TNF-α level

Although the comparison among groups showed a significant TNF-α elevation in the ischemic group, declined TNF-α level was observed in DMF 15 mg/kg group (Figure 5).

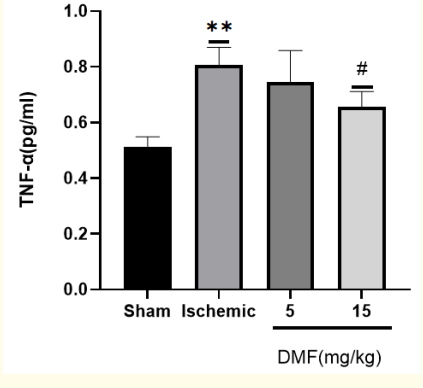

Figure 5: The effect of DMF on TNF-α level in kidney ischemia-reperfusion. The TNF-α level increased in the ischemic group (**P < 0.01 compared to the sham group) and dropped in DMF 15 mg/kg group significantly (#P < 0.05 compared to the ischemic group). Data are presented as Mean ± SEM, (N = 6).

Evaluation of NF-κB level

In the studied groups, the NF-κB factor increased significantly in the ischemic group compared to the sham group. However, the DMF 15 mg/kg could reduce the NF-κB factor significantly (Figure 6).

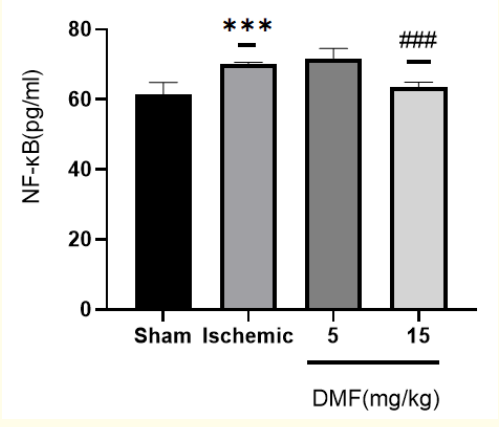

Figure 6: The effect of DMF on NF-κB level in kidney ischemia-reperfusion. The level of NF-κB increased in the ischemic group (***P < 0.001 compared to the sham group). The NF-κB level decreased in DMF 15 mg/kg group significantly (###P < 0.001 compared to the ischemic group). Data are presented as Mean ± SEM, (N = 6).

Discussion

In this study, we evaluated the effect of DMF on kidney IR in rats. Recently IR is suggested as the main cause of AKI [20]. Although AKI care is now developed a lot, still dialysis process, cost of hospitalization, and graft rejection are of concern [21]. On the other hand, the main mechanism of IR is not clear yet, however it is believed that hypoxia and nephrotic cell death are associated with the activation of inflammatory cascades and oxidative stress [22]. Following ischemia, ions such as sodium and calcium are overloaded in the cell and oxygen delivery is reduced to the tissues. Also, the oxygen is mostly converted to O_2−, which is a destructive radical for cells. Moreover, a series of reactions such as activation of NADPH oxidase, which can increase ROS production, occurs. The raised ROS plays an important role in nephron dysfunction by activating inflammatory factors, leukocytes, and platelets [23]. On the other hand, to protect the cells against ROS, anti-oxidant factors such as SOD and GSH are produced which convert O_2- to H_2O_2 and then H_2O [24]. The produced H_2O_2 can activate p38 mitogen-activated protein kinase (P38 MPA) which facilitates the activation of NF-kB and TNF-α production. Also, TNF-α stimulates the production of ROS which leads to positive feedback in an oxidant and inflammatory cycle [25].

Regarding the role of inflammatory and oxidative pathways in IR, anti-inflammatory and anti-oxidant drugs are possible

protective choices. As it is known since 2013 DMF is one of the choice drugs for MS and inflammatory diseases [15]. Mechanism of action of DMF includes stimulation of excitatory cells, reducing inflammatory cytokines, affecting translation of NF-κB, and increasing the production of cytokines such as IL-4 and IL-5 in stimulated T lymphocytes. Also, DMF has a stimulatory effect on Nrf-2 which protects cells by binding to antioxidant responsive elements in the promoter of protective genes such as 1-NADPH-quinone oxide reductase and 2-Heme-oxygenase [26]. Besides mentioned effects of DMF, it was selected for IR because of its high safety. Some of the prevalent adverse effects which do not limit the administration of the drug include flushing, abdominal pain, diarrhea, and nausea [27].

Our study confirmed the protective effects of DMF on kidney IR by reducing inflammatory cytokines and elevating anti-oxidant mediators. Following IR, the level of serum creatinine and BUN increases which indicates tissue damage and kidney impairment [25]. The experimental results of this study showed that the level of serum creatinine and BUN increased in the ischemic group, however, it declined in DMF 5 and 15 mg/kg group. As a result, the mentioned doses of DMF attenuated IR-induced damage in kidney tissues and improved their function. On the other hand, our results showed that the level of creatinine and BUN was raised by DMF (45 mg/kg) which can be reported as a side effect of a higher dose of DMF. It is thought that this dose of DMF passed through the therapeutic index for IR and as a consequence, the inflammatory and oxidant markers were not studied in this group. Regarding the protective effect of DMF on kidney IR in the clinical stage, the inflammatory and oxidative pathways were evaluated [28].

The results showed that, although the level of TNF-α and NF-Kb elevated due to IR, the 15 mg/kg DMF reduced the inflammatory markers. Similar to our study, Kinsey G.R., *et al*. showed that in renal failure the level of TNF-α is increased in response to the rising of macrophage permeability inside the tubules [29]. Moreover, during ischemia, NF-Kb, which also has a rapid onset of action, regulates cellular responses and activates inactive factors such as TNF-α, ROS, and IL-1β, within a short period [30]. Our results are in line with previous studies which showed that DMF decreased the level of TNF-α produced by B-cell and CD8+ T cells in MS [31,32]. Studies on neuroprotective effects of DMF also reported that it inhibits the NF-Kb activation through Nrf induction. Moreover, Peng., *et al*. study found that DMF reduced the expression of NF-Kb by decreasing the rate of phosphorylation and expression of p65 as well as inhibiting the kinases that regulate extracellular (ERK1/2) signals [33].

Besides inflammatory pathways, oxidant stress is also involved in IR damage. IR injuries in the kidney include changes in the morphology and function of the kidney, necrosis of the renal tubules, and disturbances in the body's water and electrolyte balance [28,34]. Despite ROS generation, SOD plays a key role in the first step of eliminating free radicals followed by IR. Also, GSH as a nucleophilic scavenger has a vital role in protecting cells from stress oxidative [35]. Evaluation of SOD and GSH changes in serum samples showed a decrease in these protective factors in the ischemic group. However, the 15 mg/kg dose of DMF prevented the reduction of these factors compared to the ischemic group. Our results are consistent with a study that demonstrated the protective effect of DMF on sepsis through activating catalase and SOD enzymes [36]. Similar to our study, Wang et.al showed that DMF increases the frequency of neurospheres and the survival of nerve cells by reducing oxidative stress. Also, it has been reported that DMF attenuates liver ischemia through anti-inflammatory and anti-oxidant pathways [37]. The anti-oxidant effect of DMF may be associated with Nrf-2 activation which is an important transcription factor that simultaneously expresses a wide range of antioxidant and detoxifying genes including oxygenase-1 and glutathione S-transferase [38].

Since the protective effect of DMF on the kidney, IR is accompanied by anti-inflammatory and anti-oxidant effects, and regarding its known pharmacokinetics, pharmacodynamics, and adverse effects, DMF can be suggested as a beneficial drug against kidney IR.

Conclusion

DMF improves the kidney IR-induced injuries by altering the stress oxidative and inflammatory cascades.

Acknowledgment

We appreciate Cinnagen Co. for providing DMF powder for this research.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethical Approval

The animal study was approved by the Research and Ethics Committee of Islamic Azad University, Tehran Medical Sciences, Tehran, Iran with an ethical code of (IR.IAU.PS.REC.1397.397).

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