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Original Article

The Effect of Gender on Brain Tissue Changes Induced by Renal Ischemia-Reperfusion Injury in Adult Rats

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Abstract

Background: Renal ischemia-reperfusion (RIR) is a common clinical injury that affects the function of other remote organs such as the brain by initiating a cascade of complex and wide-ranging inflammatory responses. RIR also follows a different course in men and women. Since there is little information on the effect of RIR on the brain as a sensitive organ in both males and females, the present research was performed to investigate the effect of gender on RIR-induced brain tissue alterations in adult rats.

Materials and Methods: In this study, 28 Wistar rats (14 female and 14 male rats) weighing 200 ± 20 g were divided into the following groups: 1- male sham (MS), 2- female sham (FS), 3- male ischemia (MI) with 3-hour reperfusion (ISC3hr), and 4- Female ischemia (FI) with 3-hour reperfusion (ISC3hr). Bilateral renal ischemia was induced for 45 minutes and blood samples were taken after reperfusion for the measurements of serum blood urea nitrogen (BUN), creatinine (Cr), malondialdehyde (MDA), and nitrite levels. The left kidney was removed for evaluation of MDA and tissue nitrite levels. Right kidney and brain tissue underwent histological examination.

Results: Serum BUN level increased in both genders. Serum nitrite level was significantly different between both genders, meaning that it was increased in the female rats as compared to male ones. Overall brain tissue damage was significantly increased in males compared to females.

Conclusion: RIR has an effect on the function and tissue of kidney and brain in both genders. Female rats are more susceptible to the nitric oxide system than the male ones. This study showed that male brain tissue was more susceptible to RIR. Therefore, gender is one of the important factors that should be considered in clinical treatments.

Keywords: Gender, Brain Tissue, Renal, Ischemia-Reperfusion Injury

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Introduction

Ischemia-reperfusion (IR) refers to a common clinical and laboratory injury in which tissue ischemia occurs with oxygen depletion followed by reperfusion, which in turn triggers a cascade of complex and extensive inflammatory responses thereby exacerbating both local injury and impairing the function of other remote organs, including the brain (1). IR is one of the main causes of acute kidney injury (AKI) in inpatients. AKI is seen in 15% of hospitalized patients and in more than 60% of Intensive Care Unit patients (2). Oxidative stress causes lipid peroxidation and increased malondialdehyde (MDA) level under renal ischemia-reperfusion (RIR) conditions. MDA has been evaluated as one of the oxidative stress factors. On the other hand, this high mortality rate seems to be mainly due to the adverse effects of AKI on remote organs, including the brain. The brain is a vital organ in the body that is severely exposed to oxidative damage due to high oxygen consumption and oxidative stress (3). The interactions between brain and kidney may be disrupted under AKI conditions by exacerbating the damage caused by cytokine secretion and leukocyte infiltration, oxidative stress, and dysregulation of sodium, potassium, and water channels. In vitro and AKI

animal models have shown that inflammatory response is associated with functional and morphological changes in vascular endothelial cells and tubular epithelium. These processes increase the penetration of leukocytes, including neutrophils, lymphocytes, and macrophages, which stimulate the production of cytokines and chemokines. Previous studies have identified significant changes in neurotransmitter levels in AKI models of Wistar rats. They include reduced levels of dopamine in the striatum, mesencephalon, and hypothalamus which can have a significant effect on learning, memory, anxiety, and depression (4). Inflammatory processes activated during ischemic AKI may lead to secondary changes in the water and electrolytes exchange, which leads to the accumulation of uremic toxins such as creatinine and guanidine. The accumulation of toxic free radicals in the bloodstream, such as reactive oxygen species and reactive nitrogen species, increases the susceptibility of brain tissue to ischemic injury and initiates many molecular cascades, which in turn leads to a maximum increase in blood-brain barrier (BBB) permeability, brain edema, hemorrhage, and brain inflammation and causes necrosis and cell death (4). It is clear that gender and sex hormones play a prominent role in kidney diseases. Men have been shown to be more susceptible than women to kidney disease and women are more resistant. Previous researches confirm the role of male and female sex hormones in creating morphological and functional differences of the kidneys. One study investigated the effect of ischaemia-reperfusion injury (IRI) in both genders and the results showed that male rats were more susceptible to post-ischemia renal failure than female rats due to androgen-induced vascular changes (5, 6). Gender affects renal IRI in various cases. Testosterone as a male sex hormone increases apoptosis in endothelial cells and renal tubular cells. Estrogen reduces endothelin-1 production, retains Na/K ATPase function through its antioxidant effects, and counteracts IRI (7). On the other hand, the nitric oxide (NO) system acts in a gender-dependent manner and NO production is higher in the systemic arteries of women than those of men. The expression of endothelial nitric oxide synthase (eNOS) and eNos mRNA is higher in females than in males (8). It has also been found in a study that ovariectomy reduces eNos levels while estrogen replacement does the vice versa. Since there has been no study on the role of gender in renal diseases and the effect of RIR on the major remote organs such as the brain in both genders, the present study examined the effect of gender on IRI-induced brain tissue injury.

Material and Methods

In this study, 28 Wistar rats (14 female rats, 14 male rats) weighting 180-220 g underwent ischemia-reperfusion surgery. Animals were kept in specific cages at animal house of the University of Hormozgan in a room with a temperature of 23 to 25°C, a 12 h/12 h light–dark circadian cycle, and free access to food and water.

Animals were divided into 4 groups (n=7 per group) as follows: 1) male sham (MS), 2) female sham (FS), 3) Male ischemia (MI) with 3-hour reperfusion (ISC3hr), and 4) Female ischemia (FI) with 3-hour reperfusion (ISC3hr). All rats in groups were weighed and anesthetized with chloral hydrate solution (450 mg/kg, ip) (9). A skin incision was made in the kidneys of the animal and the kidneys were then removed. In renal ischemia groups, the kidney vessels were completely clamped at the renal hilum for 45 minutes. Afterwards, the clamp was opened and the kidneys were returned to the body after ensuring the reperfusion (observing a normal kidney color) and the surgical area was then sutured. In sham groups, surgery was performed, but the renal artery and vein were not clamped. After 3 hours, the animals were anesthetized again and blood samples were taken from the heart to measure serum factors and finally euthanized. The kidneys and brain were then removed from the body. The right kidney and brain were placed in 10% formalin solution and sent to the pathology unit for histological tests (hematoxylin-eosin (H&E) staining method). The left kidney was also homogenized for evaluation of tissue nitrite and MDA levels. Serum blood urea nitrogen (BUN) and creatinine (Cr) levels were measured using Pars Azmoon Kit. Serum nitrite level was measured by Griess reagent method. Thiobarbituric acid reactive substances were used to measure MDA level. To evaluate renal damage, the presence of tubular atrophy, hyaline cast, congestion, necrosis, vacuolization, and inflammation were taken into account and to assess brain tissue damage, congestion, gliosis (increased glial cell proliferation), and necrosis were examined. The grade of histopathological damage was calculated. The injuries were expressed as a percentage and graded as follows: 0 (0-15%), 1 (15-25%), 2 (26-50%), 3 (51-75%), and 4 (more than 75%).

Data Analysis

One-way ANOVA and Tukey post hoc tests were used to evaluate data on blood factors (BUN, Cr, MDA, and nitrite) and renal nitrite factors. Kruskal-Wallis and Mann-Whitney tests were also used to analyze data obtained from kidney and brain tissue damage and carry out the relevant inter-group comparisons. All data were reported as mean ± SEM and a P value <0.05 was considered statistically significant. Statistical analysis was also performed using SPSS version 22.0.

Results

The Effect of Renal IRI on BUN, Cr, Kidney Tissue Weight and Kidney Tissue Injury in Male and Female Rats

Kidney weight was increased in ischemia groups compared to the sham group and it increased more significantly in male rats than in female ones. The blood BUN level increased in both genders and there was a significant difference between the sham and ischemia

groups. Creatinine levels were not significantly different in either gender of sham and ischemia groups. There was also no significant increase in the ischemia group in terms of overall kidney tissue injury (Figures 1, 4).

The Effect of Renal IRI on Serum Nitrate and Renal MDA Levels in Male and Female Rats

Serum MDA, tissue MDA, and tissue nitrite levels were not significantly different between the sham and ischemia groups in either gender. There was a significant difference between the two genders of the ischemia group in terms of the serum nitrite level and it increased only in female rats (Figure 2).

The Effect of Renal IRI on Brain Tissue in Both Genders

There was a significant difference between male rats of the ischemia and sham groups in terms of overall brain tissue injury, gliosis, and necrosis, but there was no difference in female rats. Furthermore, the congestion rate increased significantly in both genders of the ischemia group (Figures 3, 5).

Discussion

Disorders known as IR are the most common causes of debilitating diseases and death. IRI leads to tissue injury which depends on the severity and duration of ischemia and the time of reperfusion (10). The kidney and brain are two vital organs that are susceptible to IRI and gender has an inevitable impact on these two organs. According to the results, kidney weight increased in ischemia groups and it increased more significantly in males. Post-IRI kidney weight gain may be due to the retention of water and salts in the kidney tissue and renal edema due to

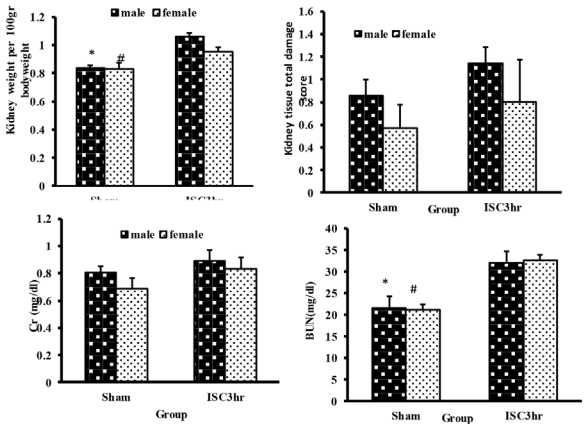

Figure 1. Comparison of Kidney Weight (KW), Kidney Tissue Damage Rate, Blood Urea Nitrogen Level (BUN) and Creatinine (Cr) in Both Male and Female Groups During Ischemia-reperfusion. * and # indicate a significant difference ($P<0.05$) between sham and ischemia in both male and female rats, respectively. Data were reported as mean ± SEM. *P* values were derived from one-way ANOVA and Kruskal-Wallis tests.

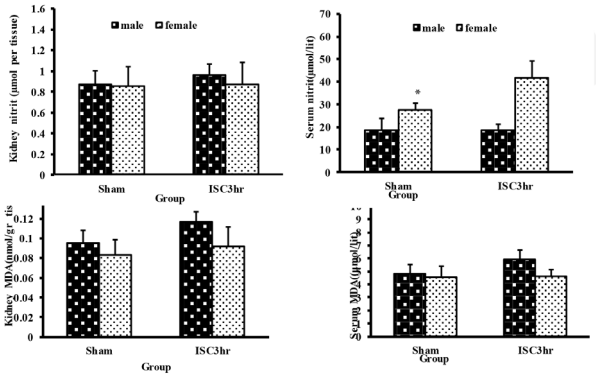

Figure 2. Comparison of Serum and Kidney MDA and Nitrite Levels in Both Male and Female Groups During Ischemia-reperfusion. * indicates significant difference ($P<0.05$) between the sham and ischemia in female rats. The data were reported as mean ± SEM. *P* values were derived from one-way ANOVA.

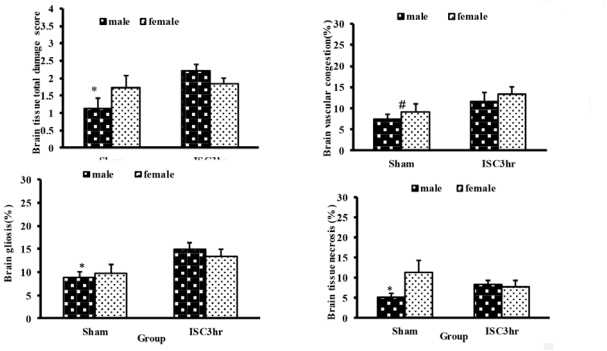

Figure 3. Comparison of Total Brain Tissue Damage, Cerebral Venous Congestion, Gliosis, and Necrosis of Brain Tissue in Both Male and Female Groups During ischemia-reperfusion. Data were reported as mean ± SEM. # indicates significant difference between sham and ischemia groups in both genders. * indicates significant difference ($P<0.05$) between sham and ischemia groups in male rats. *P*-values were derived from Kruskal-Wallis tests.

renal tubular damage or renal circulatory changes due to ischemia and cell proliferation (11). Afyouni et al and Iran-Nejad et alobserved weight gain in both genders, indicating the effect of ischemia on kidney weight as an indicator of injury (12, 13). The results showed that BUN levels increased in both genders in the ischemia groups after 3 hours; however, Cr levels did not. IRI causes kidney dysfunction in both males and females and is characterized by an increase in BUN and Cr levels (13). Ko et al used a bilateral ischemia model for 60 minutes followed by 6-hour, 1-day, and 7-day reperfusions. The results showed that Cr levels did not change 6 hours after ischemia then it increased significantly and peaked 24 hours after ischemia (14). A Cr rise of ≥0.3 mg/dL in 48 hours is considered as a criterion for the diagnosis of

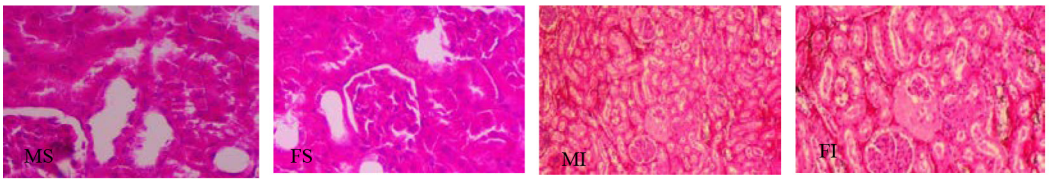

Figure 4. Comparison of Kidney Tissue in Male Sham (MS), Female Sham (FS) with Female Ischemia (FI) and Male Ischemia (MI) Groups. Tissue injury is seen in the ischemia groups.

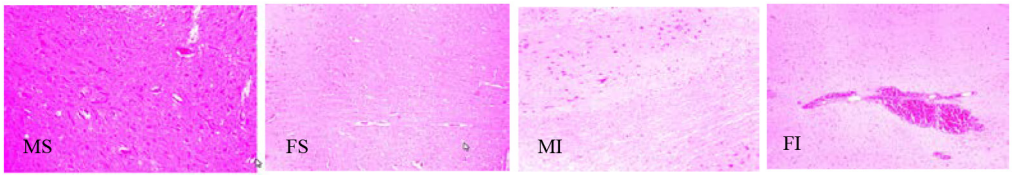

Figure 5. Comparison of Brain Tissue in Male Sham (MS), Female sham (FS) with Female Ischemia (FI) and Male Ischemia (MI) Groups. Congestion, gliosis, and necrosis are seen in the ischemia groups.

AKI. However, measuring renal function based on serum Cr levels may be an inaccurate method of diagnosing sudden kidney dysfunction because a significant increase in serum creatinine levels occurs when approximately 50% of nephrons have lost their normal function (15). Therefore, elevated serum Cr levels are dependent on the duration of reperfusion and the rate of kidney tissue injury.

The present study evaluated MDA as one of the oxidative stress factors and showed that serum and tissue MDA levels did not change significantly. Various studies have reported increased levels of MDA following renal IRI. In a study of the effect of chlorpromazine on IRI after 60 minutes of ischemia and reperfusion after 5 minutes and 24 hours, Tucci Junior et al. showed that MDA levels increased significantly within 5 minutes but returned to its normal level within 24 hours. They attributed their finding to the fact that lipid peroxidation process plays a role in renal injury at the anoxic and pre-reperfusion stages, and MDA level increases and then decreases at the beginning of the reperfusion stage (16). In the present study, the serum nitrite level increased in female rats, which may be due to the effect of female sex hormones on increased NOS expression (17). Choi et al concluded that maximal iNOS and eNOS activity occurred 2 and 4 hours after reperfusion, respectively, and their activity then showed a decreasing trend (18). Tripatara et al found that eNOS was active 6 hours after reperfusion, whereas iNOS activity did not change. (19). These studies and some others revealed that NO levels seem to increase slightly after ischemia and then decrease. Increased nitrite levels occurred in female rats in the present study and as we know, NO activity is gender-dependent. NO production in the systemic vessels is higher in females than in males. It is also produced at higher levels during pregnancy when estrogen levels are high. The levels of mRNA and renal eNOS protein are higher in females than in males (8). Generally, nitric oxide production is higher in females than in males; therefore, this pathway may be more affected under hypoxic conditions, which is consistent with the present study, indicating that the nitrite level, as an indicator of nitric oxide production in the female, increased in the early stages of reperfusion.

The present study showed that two genders were differently affected by IRI-induced kidney and brain tissue injuries, and the males were affected more significantly. Müller et al showed that kidney tissue injury was similar in both genders 2 hours after ischemia and was not significantly different (20). Overall, previous studies showed that male rats are more susceptible to renal IRI than female ones, and testosterone increases renal ischemia in rats but female sex hormones play a protective role (5, 6). In this study, overall brain tissue injury and gliosis and brain tissue necrosis significantly increased in male rats, but this increase was not significant in females. Cerebral venous congestion significantly increased in both genders. In addition, aquaporins are largely expressed in the brain and cause brain edema following AKI (4). Edema can put pressure on the brain vessels and cause congestion. The rate of gliosis indicates the inflammatory status of the brain. Consistent with the present study, Liu et al examined the effect of AKI on the brain of the mouse model of renal IRI. After 60 minutes of ischemia and 24 hours of reperfusion, increased microglial cells, inflammation in some areas, and pyknotic neurons in the hippocampus were observed. They found elevated serum and cellular inflammatory proteins (21). Mohamed and Mubarak observed brain inflammation and pyknosis

in neurons after 60 minutes of bilateral renal ischemia and then 1 hour of reperfusion (22). Chou et al also found severe inflammatory brain injury after 60 minutes of bilateral ischemia and then 2 hours and 24 hours of reperfusion, including an increase in the number of activated microglial cells (23). Experimental evidence has shown that AKI causes systemic inflammation and that the AKI-induced inflammatory reactions lead to impaired BBB, endothelial damage, stimulation of inflammatory, and coagulation cascade. This process is characterized by activation of microglia, astrocytes, neurons, and endothelial cells, increase of BBB permeability, and the entry of peripheral immune cells into the brain tissue, secretion of inflammatory cytokines, neuronal injury, and death (24). It also leads to oxidative stress in the brain (25). A post-AKI increase in reactive oxygen species, NO, and inflammatory mediators is associated with neurotoxicity and neuronal death.

The results of recent studies on the effects of gender show that ovarian steroids have protective functions on the central nervous system. The steroid crosses BBB easily and reaches the nerve tissue because it is lipophilic and has a low molecular weight. The most well-known neurological effect of steroid hormones includes their ability to protect against damage to the central nervous system such as stroke. Estrogen triggers nitric oxide production, which is associated with the dilation of blood vessels. This action increases blood flow to risky brain areas (26).

Conclusion

The current finding indicates that the gender as a key factor should be considered in clinical therapy. Moreover, females are more resistant to RIR, however male gender shows greater susceptibility to brain injury induced by renal IR. This gender difference may relate to NO system that is affected by sex hormone.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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Ethical Statement

This article is taken from a research project which was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1397.159).

Authors' Contribution

AD, FAr, and FAz performed the majority of this work such as application of experimental design ideas, implementation of the research, preparation of the manuscript, the interpretation of the data and data analyses. AAAP performed histopathological investigation. All authors discussed the results and contributed to the final manuscript.

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Informed Consent

This item was not included in this project.

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