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Prazosin Treatment Protects Brain and Heart by Diminishing Oxidative Stress and Apoptotic Pathways After Renal Ischemia Reperfusion

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ABSTRACT

Acute kidney injury (AKI) is a major medical challenge caused from renal ischemia-reperfusion (IR) injury connected with different cellular events in other distant organs. Renal IR-related oxidative stress and inflammation followed by cell apoptosis play a crucial role in IR-induced distant organ pathological damages. Prazosin has shown protective effects against IR-injuries. Thus, the current study intended to investigate the possible protective role of prazosin against the consequents of renal IR in the heart and brain tissues. To reach this goal, rats were randomly divided into 3 groups (n = 7): Sham, IR and prazosin pretreatment-IR animals (1 mg/kg intraperitoneally injection of prazosin 45 min before IR induction). After 6 h reperfusion, lipid peroxidation and antioxidant markers levels were evaluated in the both, brain and heart tissue. Moreover, apoptotic pathway in the heart and brain tissues were assessed by western blotting. Accordingly, prazosin pretreatment in IR model rats could significantly increase the antioxidant capacity and attenuate apoptotic pathways by increasing the bcl-2 levels and decreasing the expression of Bax and caspase 3 enzymes ($P < 0.05$). Thus, prazosin suppressed cellular damages of heart and brain tissues post kidney IR by anti-oxidative and anti-apoptotic effects, which suggests the plausible use of prazosin in improving the clinical outcomes during AKI after further investigations.

Introduction

Acute kidney injury (AKI) is a major, rapidly increasing public health concern connected with morbidity, high mortality risk and economic impact particularly in developing countries [1, 2]. Renal ischemia reperfusion (IR) is a histopathological condition that contributes to AKI, occurs typically in renal artery stenosis, trauma, following a shock of any kind and renal transplantation [3, 4]. During renal I/R, excess amount of reactive oxygen species (ROS) generated by injured tissue, mitochondrial oxidative suppression caused by lack of oxygen, ATP phosphorylation depletion, increased

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intracellular calcium, and peroxidation of membrane leads to apoptosis and triggers inflammatory cascades [5–7]. Although reperfusion is the survival stage for providing oxygen and substrate for the production of ATP to the ischemic tissue, but interestingly reperfusion itself causes additional tissue impairment by generation of extra free radicals [8]. AKI-induced distant organ cross talk shows important roles in other organs dysfunction and deleterious vital effects such as respiratory complications, cardiorenal syndrome (CRS), hepatorenal syndrome (HRS), neurological complications, systemic sepsis, and polymicrobial peritonitis [9, 10]. Fluid overload contributes to hydrostatic alveolar edema as the main cause of lung dysfunction in AKI, and attenuates performance of myocardium [11, 12]. Uremic toxin accumulation during AKI was observed to be accompanied by encephalopathy, irritability, loss of memory, seizures, attenuated mental status, functional complications in locomotor activities and other neurologic impairments [11, 13]. Furthermore, the accumulation of neurotoxic metabolites can result in blood brain barrier damage and infiltration of these toxic metabolites into the brain [12]. Metabolic acidosis and disruption in electrolyte balance mediate cardiovascular complications such as myocardial contractility and arrhythmias[14]. Moreover, recent clinical studies have demonstrated that AKI induces cardiovascular dysfunction via various mechanisms including unsteady renin-angiotensin-aldosterone system (RAAS), and sympathetic nervous activation [14–16]. Increased renal sympathetic nerve activity leads to RAAS activation through a reno-cerebral reflex [17, 18]. This kidney-brain interaction arises overproduction of oxidative stress and systemic inflammation [19]. Increased oxidative stress significantly promotes the generation of RAAS from the ischemic tissue and has an obvious role in distant organs dysfunction in AKI-induced organ-organ crosstalk [20]. Controlling the blood pressure, RAAS inhibitors, blockage of renal sympathetic nerve activity and administration of sympatholytic drugs may protect against ROS formation and systemic inflammation [19]. Although the underlying mechanism is vague, increased oxidative stress is one of the obvious pathways leading to uremic encephalopathy [21]. Furthermore, there are many evidence showing that oxidative stress is tightly connected with the induction of apoptotic machinery by production of ROS and depletion of the cellular antioxidant capacity [22, 23]. Extrinsic and mitochondrial pathways are two major pathways of apoptosis activation. One of the important factor of extrinsic pathway of apoptosis is a protease, caspase-3, which causes cytotoxicity through proteolysis in injured cells [8, 24]. In the mitochondrial pathway, over expression of pro-apoptotic factors and down regulation of anti-apoptotic factors leads to the fragmentation of mitochondria, and subsequently cell death in a process called mitoptosis [25, 26]. Prazosin, a potent α1-adrenergic receptor antagonist, synergistically expands the peripheral arteries and regulates antihypertensive action [27–29]. Prazosin prevents cerebral infarction by inhibition of the inflammatory cascade [27]. Accordingly it is hypothesized that prazosin as a known sympatholytic medicine, may alleviate AKI after renal IR damage. In the current project, the effects of prazosin on IR-associated disturbances in vital distant organs including the brain and heart were assessed *in vivo*. Moreover, bearing in mind the important role of heart and brain in regulating every process in human's body, we assessed the impact of apoptosis pathways in cardiac and cerebral tissue using western blot assay.

Material and methods

Reagent

Prazosin was purchased from Tocris Bioscience (Ellis ville, Mo) and dissolved in distilled water for intraperitoneal injection. Western blotting-related primary and secondary antibodies were provided from Thermo Fisher Scientific – US. The other used reagents were prepared form standard commercial suppliers.

Animals

In this empirical investigation, 21 healthy adult male wistar rats (230 ± 15 g) were obtained from Pasture Institute (Tehran, Iran). In order to adapt with the condition, they were maintained in an average ambient temperature of 21 ± 2 °C, 60 ± 5 % humidity and 12 h light/12 h dark cycle under the same environmental and nutritional condition for 7 days with food and water ad libitum. The animal experiments were performed according to the standards of the National Institute of Health for Laboratory Animals Care and Use (IR.TBZMED.VCR.REC.1399.300).

Experimental groups

Animals were randomly separated into three groups of seven animals: sham group, non-treated IR group and prazosin (1 mg/kg) pre-treated IR group [7, 30]. Briefly, Group III received prazosin 30 min preceding the IR induction but the other two groups got no treatment.

Induction of ischemia reperfusion injury

Intraperitoneal administration of xylazine (10 mg/kg) and ketamine (90 mg/kg) was utilized to anesthetize the animals [7] and unilateral IR was induced [31]. In brief, the abdominal region was incised in all groups, whereas renal vascular was manipulated in sham group without clamping. In the other two groups renal vascular were clamped for 45 min. Successful ischemia was evaluated by transforming the color of the renal tissue to pale. Blood specimens were taken directly from the left ventricle after 6 h reperfusion. Subsequently, rats were euthanized, the brain and heart tissues were dissected and maintained at − 80 °C until biochemical assays were done.

Biochemical analyses

In order to perform biochemical analysis, small pieces of the rat's heart and brain were placed in a cold sucrose (0.25 M) solution, and then a filter paper was used to blot them. Then, tissue homogenizer (Remi Motors, Mumbai, India) was utilized to homogenize the tissues in cold tris-hydrochloride buffer (10 %), which was followed by a centrifugation step (7000 rpm for 15 min at 0 °C), and the produced supernatant was applied to measure malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT) activity, reduced glutathione (GSH), glutathione peroxidase (GPx), and total antioxidant capacity (TAC).

MDA as a lipid peroxidation end product was evaluated spectrophotometric measurement of thiobarbituric acid reactive substanc-

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es [32]. SOD activity in cardiac and cerebral tissue was evaluated based on the prohibition of pyrogallol auto-oxidation by SOD, as previously established by Marklund and Marklund [33]. The activity of CAT was assessed according to the Claibone technique [34]. The essay is based on spectrophotometric measurement of the decomposition rate of hydrogen peroxide. Subsequently, GPx activity was assayed using commercial kit [35, 36]. GSH level was detected by the method previously described as Nm/MG-PRnm [37].

Western blotting

To determine the effect of prazosin on apoptosis cascade in cardiac and cerebral tissue, apoptosis-associated factors (pro and cleaved caspase-3, Bcl-2, Bax) were assessed using western-blot analysis as described previously [38, 39]. Protease-inhibiting cocktail-encompassed cold PIPA lysis buffer was used to homogenize cardiac and cerebral tissues. The homogenate was centrifuged at 12000 rpm for 10 min and a BCA protein assay kit (Pierce Bio chemical, Rockford) was applied to evaluate the level of total protein. Then, protein separation on SDS-PAGE (10 %) and subsequently transfer to polyvinylidene fluoride membrane was performed [40] followed by blocking with the skim milk (5 %) and incubation with primary antibodies at 4 °C overnight namely mouse Monoclonal Bcl-2 (cat. No. sc-492), Bax (cat. No. sc-7480), caspase-3 (cat. No. sc-7272) and cleaved caspase (cat. No. sc-56052). After washing the membrane with Tris-buffered saline–tween20 (TBST) 3 times for 5 min each, the membrane was incubated with goat anti-mouse HPR-conjugated antibody (cat. No. sc-2031) as a secondary antibody at room temperature for 2 h. Enhanced chemiluminescence detection kit (Roch, UK) was used to visualize the bands. In final stage, densities of blots were measured by the image J 1.6 software and each protein bond has been normalized using B-actin control.

Statistical analysis

All data were represented as the mean ± SEM. Graph pad prism software 6.01 software was utilized to do statistical analysis. One-way analysis of variance (ANOVA) followed by Tukey's test was uses to determine significance. $P < 0.05$ was considered as statistical significant level.

Results

The effect of prazosin on lipid peroxidation parameters after renal IR

As shown in ▶ **Table 1** and ▶ **2**, non-treated IR rats had dramatically higher MDA level in the heart and brain tissues in comparison to the sham group ($P < 0.001$), while prazosin pretreatment substantially reduced of MDA levels in the brain and heart tissue in the IR injured rats ($p < 0.01$, $P < 0.001$).

The effect of prazosin on oxidative stress parameters in the brain and heart tissues after renal IR

As demonstrated in ▶ **Table 1**, in comparison with the sham group, I/R injury considerably plummeted the antioxidant capacity of TAC (9.24 ± 0.14 vs 11.62 ± 0.24, $P < 0.001$), GSH (7.96 ± 0.17 vs 11.39 ± 0.23, $P < 0.001$), GPx (23.48 ± 0.56 vs 28.98 ± 1.17, $P < 0.01$), CAT (33.75 ± 0.46 vs 39.42 ± 0.43, $P < 0.001$) and SOD (11.88 ± 0.19 vs 12.95 ± 0.27, $P < 0.001$) activities in cerebral tissue. Pretreatment with prazosin could significantly elevate GSH levels in the treated IR rats in comparison with IR group (9.04 ± 0.27 vs 7.96 ± 0.17, $P < 0.05$).

Following renal IR injury a dramatic fall was observed in antioxidant capacity of TAC (13.42 ± 0.36 vs 23.34 ± 0.42, $P < 0.001$), GSH (8.52 ± 0.45 vs 13.89 ± 0.76, $P < 0.001$), GPx (32.42 ± 1.34 vs 53.17 ± 2.41, $P < 0.001$) levels and CAT (55.02 ± 3.16 vs 86.74 ± 2.47, $P < 0.001$) and SOD (11.14 ± 0.38 vs 15.96 ± 0.8, $p < 0.001$) activities in cardiac tissue compared with the sham group, While pretreatment with prazosin could dramatically improve GSH (9.86 ± 0.75 vs 8.52 ± 0.45, $P < 0.05$) and catalase (67.20 ± 3.36 vs 55.02 ± 3.16, $P < 0.05$) levels in cardiac tissue ($P < 0.05$) (▶ **Table 2**).

The effect of prazosin on brain cell apoptosis after renal IR

The effect of prazosin on apoptosis-associated factors was investigated in all experimental groups. Compared to the sham group, renal IR led to remarkable increment of Bax level ($P < 0.001$), while a significant downward trend of Bcl-2 expression was observed ($p < 0.01$) (▶ **Fig. 1a–c**). However, prazosin failed to significantly affect the Bax and Bcl-2 levels. The levels of caspase-3 was meaningfully enhaned in IR rats in comparison with the sham group ($P < 0.001$), whereas compared with IR group, prazosin reduced protein level of caspase-3 ($P < 0.05$) (▶ **Fig. 1d**).

The effect of prazosin on cardiac cell apoptosis after renal IR

I/R injury was shown to be significantly in association with elevated Bax and caspase-3 protein levels compared to the sham group ($P < 0.01$), whereas prazosin treatment meaningfully plunged the levels BAX and caspase-3 in the heart tissue ($P < 0.05$) (▶ **Fig. 2b** and **d**). Moreover, I/R group exhibited diminished levels of Bcl-2 in comparison with the sham group ($P < 0.01$), while prazosin pretreatment could substantially reverse Bcl-2 expression at protein level ($p < 0.05$) (▶ **Fig. 2c**).

▶ **Table 1** The effects of prazosin on the oxidative stress parameters of rat brain tissue after renal IR.

Brain	SOD (U/mg protein)	GPX (U/mg protein)	MDA (nmol/mg protein)	TAC (µmol/mg protein)	GSH (nmol/mg protein)	Catalase (U/mg protein)
Sham	12.95 ± 0.27	28.98 ± 1.17	183.20 ± 5.53	11.62 ± 0.24	11.39 ± 0.23	39.42 ± 0.43
I/R	11.88 ± 0.19***	23.48 ± 0.56**	332.72 ± 5.28 ***	9.24 ± 0.14***	7.96 ± 0.17***	33.75 ± 0.46***
IR + prazosin	12.06 ± 0.16	25.78 ± 0.41	280.76 ± 9.42##	9.89 ± 0.27	9.04 ± 0.27#	34.79 ± 0.51

All values are mean ± SEM. * /# P < 0.05, ** /##P < 0.01, and *** /###P < 0.001. *I/R group *vs*. Sham; # prazocin-treated group *vs*. IR group. Ischemia-reperfusion (I/R); superoxide dismutase (SOD); glutathione peroxidase (GPX); malondialdehyde (MDA); Total antioxidant capacity (TAC); glutathione (GSH).

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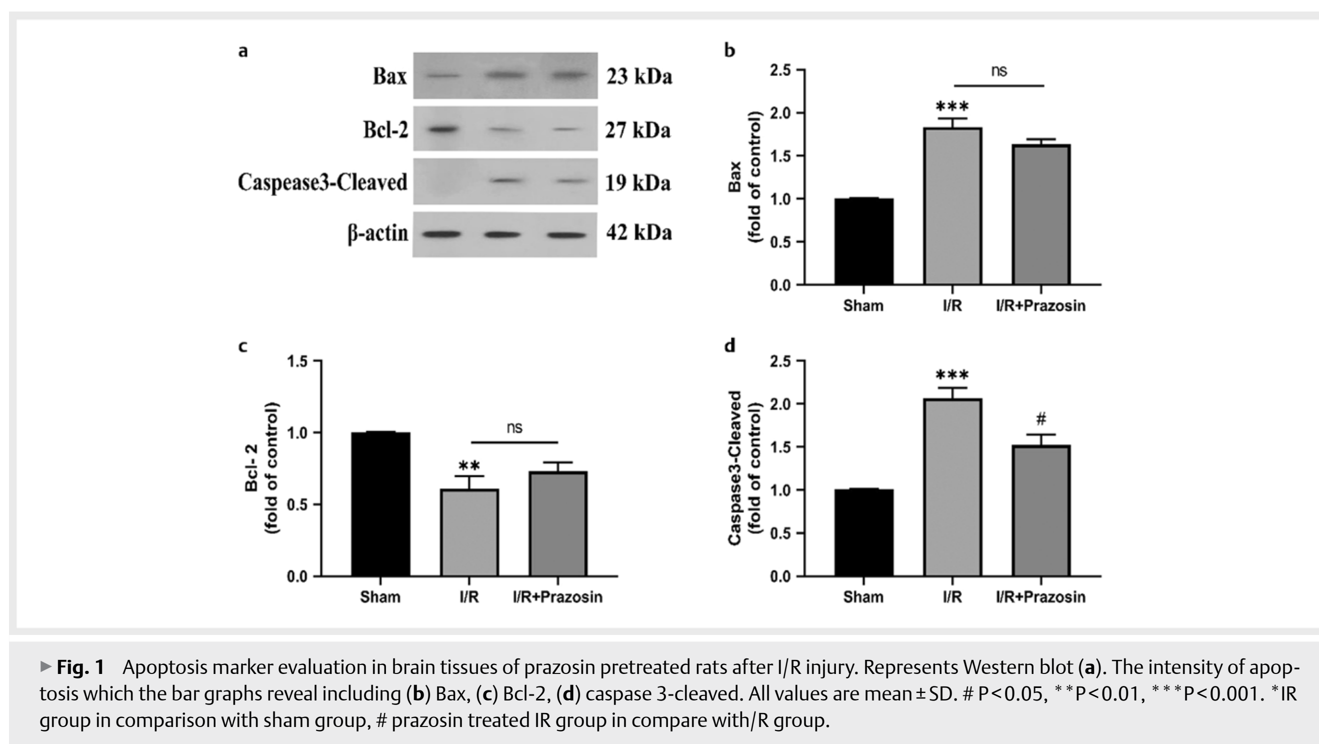
▶ **Table 2** The effects of prazosin on the oxidative stress parameters of rat cardiac tissue after renal IR.

Heart	SOD (U/mg protein)	GPX (U/mg protein)	MDA (nmol/mg protein)	TAC (μmol/mg protein)	GSH (nmol/mg protein)	Catalase (U/mg protein)
Sham	15.96 ± 0.87	53.17 ± 2.41	276.33 ± 20.49	23.34 ± 0.42	13.89 ± 0.76	86.74 ± 2.47
I/R	11.14 ± 0.38***	32.42 ± 1.34***	845.65 ± 19.96***	13.42 ± 0.36***	8.52 ± 0.45***	55.02 ± 3.16***
IR + prazosin	11.89 ± 0.34	34.17 ± 1.62	465.74 ± 23.74 ###	14.07 ± 0.38	9.86 ± 0.75#	67.20 ± 3.36#

All values are mean ± SEM. */# P < 0.05, **/##P < 0.01, and ***/###P < 0.001. *I/R group vs. Sham; # prazocin-treated group vs. IR group. Ischemia-reperfusion (IR); superoxide dismutase (SOD); glutathione peroxidase (GPX); malondialdehyde (MDA); Total antioxidant capacity (TAC); glutathione (GSH).



▶ **Fig. 1** Apoptosis marker evaluation in brain tissues of prazosin pretreated rats after I/R injury. Represents Western blot (**a**). The intensity of apoptosis which the bar graphs reveal including (**b**) Bax, (**c**) Bcl-2, (**d**) caspase 3-cleaved. All values are mean ± SD. # P < 0.05, **P < 0.01, ***P < 0.001. *IR group in comparison with sham group, # prazosin treated IR group in compare with/R group.

Discussion

In the medical setting, renal IR injury is among the most prevalent causes of AKI, associated with remarkably distant organ dysfunction including vital organs [11]. Since prominent hallmarks of IRI-induced injury in the renal tissue and also other distant organs are oxidative stress and inflammation, interventions that target and improve this signs would be beneficial in reduction of the pathological effects of I/R damage [5, 39]. In the current investigation, prazosin pretreatment shows significant improvement in the antioxidant capacities of heart and brain tissue against renal I/R-related oxidative hazard. Furthermore, prazosin could attenuate apoptotic mediators in heart and brain tissue. Mounting data has shown the therapeutic efficiency of α1-AR antagonists in the renal tissue to combat I/R injury [41]. For instance, doxazocin has been shown to protect against renal IR injury via decreasing oxidative stress, nitric oxide, and inducible nitric oxide synthase. Also, doxazosin treatment could significantly attenuate hypoxia-inducible factor 1 alpha and downregulate sodium-glucose cotransporter-2 [42]. It is reported, prazosin, a selective α1-adrenoceptor antagonist, could effectively decrease creatinine and urea as a marker of renal dysfunction. Also, prazosin pretreatment could attenuate inflammation, oxidative stress and apoptosis mediators in the renal tissue after IRI [7]. The potential protective effects of prazosin in the context of its antioxidant and anti-inflammatory impacts has also been reported. For instance, prazosin protects against drug-induced toxicity by reducing oxidative stress [43]. Moreover, the anti-inflammatory effects of prazosin has been documented since it can specifically target inflammatory mediators [44].

AKI-induced organ-organ cross talk cause several serve complications in the other distant organs specially in heart, brain, lungs and liver [45]. Distant organ cross talk after AKI cause a significant increase in oxidative stress mediators which can directly change the structure of biomolecules in distant organs cell. One of the suggested reasons of uremic encephalopathy is local oxidative stress in cerebral tissue and the renal failure could increase systemic oxidative stress [21, 46]. Evidences reports that renal I/R increase lipid peroxidation index, MDA level, in the hippocampus tissue of rats. Moreover, the level of antioxidant capacity of the hippocampus tissue decreased after renal IR [47]. Also, AKI promotes the expression of inflammatory mediators that could target the cardiovascular system in particular the myocardium of the heart with directly involvement of immune system [48] . However, a previous study

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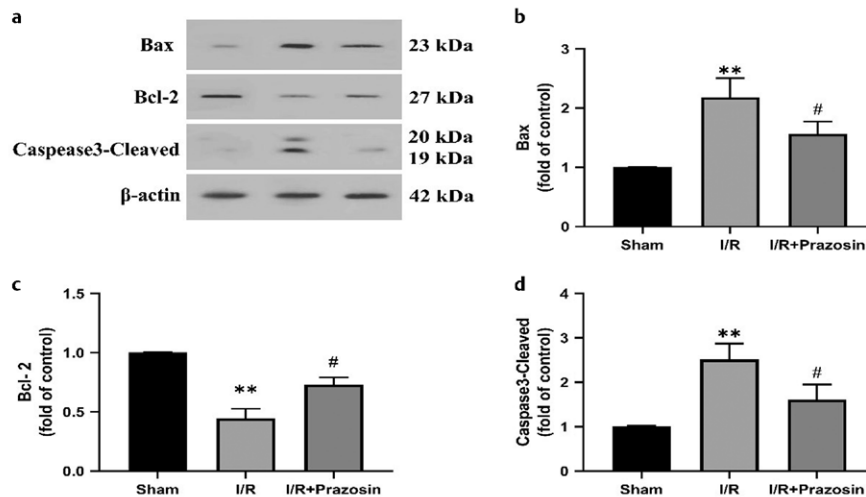

▶ **Fig. 2** Apoptosis marker evaluation in cardiac tissues of prazosin pretreated rats after I/R injury. Represents Western blot (**a**). The intensity of apoptosis which the bar graphs reveal including (**b**) Bax, (**c**) Bcl-2, (**d**) caspase 3-cleaved. All values are mean ± SD. # P < 0.05 * * P < 0.01. * /R group compared to the sham group, # prazosin treated I/R group in comparison with IR group.

has reported that I/R significantly elevates MDA level, while GSH as a central scavenger of free radicals in cardiac tissue [49]. In our study prazosin pretreatment 1 h before renal I/R could remarkably increase GSH level and decrease MDA level in the heart and brain tissue.

The main source and target of ROS is mitochondria, which modulate signaling mechanisms of apoptosis [50]. Bcl-2 Family apoptotic proteins, proteins located in mitochondrial membrane, are divided into two types: pro-apoptotic proteins (such as Bax) and anti-apoptotic proteins (such as Bcl-2) [51]. Bcl-2 as an anti-apoptotic cytokine could inhibits apoptosis by blocking permeability of mitochondrial membrane and caspase enzymes activity, thereby inhibiting free radicals to increase intracellular calcium [52]. In the other hand Bax up-regulation can promote the apoptotic pathway. It seems that Bax/Bcl-2 ratio could be a direct reflection of cell apoptosis [53]. It is reported that the renal ischemia reperfusion could dramatically decrease expression of Bcl-2 and increase expression of Bax in the brain tissue of I/R rats [54]. Although evidences reports that male rats subjected 45 min of kidney ischemia indicate increasing connective tissue in the heart muscles myofibrils as a sign of tissue injury and apoptosis of myofibrils after 24 h reperfusion following kidney I/R [55]. Losing mitochondrial outer membrane could release cytochrome C and other mitochondrial proteins in cytosol which can activate apoptotic caspases such as the main executive protease: Caspase 3 [56]. Anti-apoptotic effects of prazosin has been previously reported. For instance, prazosin inhibits apoptosis of endothelial progenitor cells via diminishing the expression of the Akt/NF-κB signaling cascade in a cerebral infarction model in vivo [57]. Mitochondrial apoptotic pathway is reversed by hindering caspase 3 and moderating Bcl-2/Bax pathway after prazosin administration in kidney tissue after kidney I/R [7]. Furthermore, our study reports that prazosin could significantly diminish apoptosis by increasing the expression of bcl-2 and down-regulation of Bax and caspase3-cleaved.

Conclusion

Results of present study indicated that prazosin pretreatment decrease lipid peroxidation and increase the level of GSH as a scavenger of free radicals on the both, heart and brain tissue and the activity of CAT enzyme in heart tissue after renal IRI. And also prazosin administration before IR could remarkably diminish the apoptotic pathway by elevating Bcl-2 and down-regulation of Bax and caspase3 enzymes.

Author contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zahra Malekinejad, Shadi Aghajani, Mostafa Jeddi, Reihane Gahremani, Sina Shahbazi. The first draft of the manuscript was written by Yasin Bagheri. Elham Ahmadian edited the final version of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The authors do agree to make all data and the statistical information available for review if required.

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Conflicts of Interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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