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Dexmedetomidine protects against ischemia and reperfusion-induced kidney injury in rats by inhibiting the expression of TRPM2 and TRPA1 channels

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ABSTRACT

Objective(s): Renal ischemia and reperfusion (I/R) injury is a potentially serious issue encountered during various medical and surgical procedures. This condition is clinically significant because of its high incidence and mortality rate. In this study, we aimed to investigate the protective effect of dexmedetomidine (DEX) on oxidative stress-activated TRPM2 and TRPA1 channel expression in rats with a renal I/R model.

Materials and Methods: A total of 35 rats were used in the study. The animals were divided into five groups. The control group received no procedure during the experiment. In the sham group, the abdomen was opened under general anesthesia, the right kidney was removed, and the left renal pedicle was exposed; however, a renal clamp was not applied. The dexmedetomidine group received dexmedetomidine, using the same surgical procedure. In the I/R groups, rats were subjected to left renal ischemia for 30 min followed by 45 min of reperfusion. Dexmedetomidine was not administered to the I/R group, while dexmedetomidine was given to the I/R+DEX group at the beginning of reperfusion. TRPM2 and TRPA1 levels were analysed in serum and kidney tissues at the end of the experiment.

Results: A significant increase in TRPM2 and TRPA1 expression was observed in all samples from the I/R group compared to the non-I/R groups, while a significant decrease in TRPM2 and TRPA1 expression was seen at the I/R+DEX compared to the I/R.

Conclusion: Dexmedetomidine may have renoprotective effects in I/R injury by inhibiting redox-TRP channels.

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Introduction

After ischemia, hypoxic tissue damage occurs due to limited energy substrate and oxygen supply. During reperfusion, mitochondrial-derived reactive oxygen species (ROS), particularly those released by polymorphonuclear leukocytes (PMNs) that migrate to and settle in the tissue, exacerbate tissue damage. Transient receptor potential melastatin 2 (TRPM2), transient receptor potential vanilloid 1 (TRPV1), and transient receptor potential ankyrin 1 (TRPA1), which are redox-sensitive transient receptor potential (Redox-TRP) channels, respond to ROS and are activated directly or indirectly by oxidative products (1).

The high oxygen consumption of renal cells makes them more vulnerable to ischemia, and reperfusion can increase cellular damage. Renal ischemia/reperfusion (I/R) injury is a common phenomenon that occurs in various diseases and surgical procedures. It is the leading cause of acute kidney injury (AKI), a condition with high mortality and morbidity (2).

Dexmedetomidine is a selective alpha-2 adrenoceptor agonist. It is used for sedation in the operating room, non-operating room anesthesia, and the intensive care unit. Studies have reported positive histopathological effects on protection against focal ischemia, renal I/R injury, incomplete forebrain ischemia, and cardiac I/R injury (3-6). Despite its increasing clinical use, the effect of dexmedetomidine on redox-TRP channels in renal I/R injury remains unclear.

This study aimed to investigate the effects of dexmedetomidine on the expression of redox-TRP cation channels and the oxidant-antioxidant balance in a rat model of renal I/R injury.

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Materials and Methods

This study was ethically approved by the decision of the Animal Experiments Ethics Committee dated 26.11.2021 and numbered 425863, and was conducted at the University Experimental Research Center and the Faculty of Medicine, Histology and Embryology laboratory. All histoscores and TUNEL evaluations were performed by an experienced histologist who was blinded to the experimental groups.

Formation of experimental groups

Thirty-five male Wistar Albino rats weighing between 200 and 230 g and 8-10 weeks old were divided into five groups of 7 rats per group.

Control group: No procedure was performed during the experimental period.

Sham group: The rats in this group were positioned supine, and the abdomen was opened via a midline incision while maintaining sterile conditions. Intra-abdominal structures that obstructed the view of the right kidney were removed. The right renal peduncle was clamped with 3-0 silk, and the right nephrectomy was performed after controlling bleeding. After exposing the left renal peduncle, no ischemia protocol was applied, and the subjects were euthanized by decapitation under deep anesthesia by approaching through the left renal tissue and diaphragm, with serum samples taken via intracardiac puncture.

DEX group: The rats in this group were placed in a supine position, and their abdomen was opened via a simple midline incision while maintaining sterile conditions. Intra-abdominal structures obstructing the view of the right kidney were removed. Once the right renal peduncle was clamped with 3-0 silk sutures and bleeding was controlled, the right nephrectomy was performed. The left renal peduncle was then exposed, and no ischemia protocol was applied. Rats received dexmedetomidine hydrochloride at 100 µg/kg intraperitoneally, and the abdomen was closed with 3-0 silk. After 45 min, the abdomen was reopened, and the subjects were euthanized by decapitation under deep anesthesia. A serum sample was collected via intracardiac puncture using a left kidney-tissue and diaphragm approach.

I/R group; Ischemia and reperfusion were maintained according to literature **(7)**. The rats in this group were placed in a supine position, and the abdomen was opened with a simple midline incision while maintaining surgical sterility. Intra-abdominal structures that hindered visualization of the right kidney were removed. The right renal peduncle was clamped with 3-0 silk, and the right nephrectomy was performed after controlling bleeding. Once the left renal peduncle was exposed, the left renal artery and vein were clamped. The abdomen was closed with 3-0 silk, and the ischemia protocol was applied. After 30 min, the abdomen was reopened, the renal clamps were removed, and reperfusion was initiated. The abdomen was then closed again with 3-0 silk. After 45 min, the abdomen was reopened, and the subjects were euthanized by decapitation under deep anesthesia by intracardiac puncture, obtaining serum samples through the left kidney tissue and diaphragm.

I/R+DEX group: The rats in this group were fixed in a supine position, and the abdomen was opened through a simple midline incision while maintaining surgical sterility. The intra-abdominal intestines were removed, and the right renal peduncle was clamped with 3-0 silk to control bleeding, followed by right nephrectomy. After exposing the left renal peduncle, the left renal artery and vein were clamped. The abdomen was then closed with 3-0 silk, and the ischemia protocol was applied. After 30 min, the abdomen was reopened, and the renal clamps were released to allow reperfusion. During this period, dexmedetomidine hydrochloride was administered intraperitoneally at 100 µg/kg. The abdomen was closed again with 3-0 silk, and after 45 min, it was reopened and serum sampling via intracardiac puncture, approaching from the left kidney tissue and diaphragm.

Collection of tissue samples

In all groups, rats were euthanized by decapitation under deep anesthesia with ketamine (75 mg/kg)+xylazine (10 mg/kg) intraperitoneally. After decapitation, the kidney tissues of the rats were rapidly removed. Serum samples were also collected via an intracardiac approach through the diaphragm. Kidney tissues were stored at -80 ˚C until the end of the study for the assessment of TRPM2 and TRPA1 expression and oxidant and antioxidant levels. For histologic analysis, kidney tissues from each group were fixed in formalin solution and then dehydrated using a routine histologic processing series (Table 4). The tissues were then cleared in xylene and embedded in paraffin blocks.

Biochemical study

Serum samples were analyzed for TAS, TOS, TRPM2, and TRPA1 (respectively) using the following kits: AD3283Ra (AndyGene Biotechnology Co., Ltd., Beijing, CHINA), AD3282Ra (AndyGene Biotechnology Co., Ltd., Beijing, CHINA), Rat TRPM2 ELISA kit (SunRed 201-11-6173, China), and Rat TRPA1 ELISA kit (SunRed 201-11-6652, China). The analyses were conducted using ELISA, according to the procedures outlined in the manufacturer's kit manuals (8). Positive controls supplied with the ELISA kits were used, and all assays were validated by generating standard curves and performing duplicate measurements.

Immunohistochemical study

The sections, 4-6 mm thick, were transferred from paraffin blocks to polylysine slides. Deparaffinized tissues were processed through a graded alcohol series and then boiled in a citrate buffer solution at pH 6 in a microwave oven (750 W) for 15 min to facilitate antigen retrieval. After boiling, the tissues were allowed to cool at room temperature for approximately 20 min, washed with PBS (Phosphate Buffered Saline, P4417, Sigma-Aldrich, USA) for 3x5 min, and incubated with hydrogen peroxide blocking solution for 5 min to inhibit endogenous peroxidase activity (Hydrogen Peroxide Block, TA-125-HP, Lab Vision Corporation, USA). The tissues were then washed with PBS for 3x5 min, treated with Ultra V Block (TA-125-UB, Lab Vision Corporation, USA) for 5 min to prevent nonspecific staining, and incubated with 1/200 diluted primary antibodies against TRPA1 and TRPM2 (Anti-TRPA1 antibody, FNab09013, Finetest China and Rabbit Anti-TRPM2 antibody, ab101738, Abcam, Cambridge, UK) for 60 min at room temperature in a humid chamber (9).

After incubation with the primary antibody, the tissues were washed three times for five minutes each in PBS. They were then incubated with secondary antibody (biotinylated Goat Anti-Polyvalent, TP-125-BN, Lab Vision Corporation, USA) for 30 min in a humidified environment

at room temperature. Next, the tissues were washed three more times with PBS for five minutes each, followed by incubation with Streptavidin Peroxidase (TS-125-HR, Lab Vision Corporation, USA) for 30 min under the same conditions. Afterward, they were rinsed in PBS and treated with 3-amino-9-ethylcarbazole (AEC) Substrate plus AEC Chromogen (AEC Substrate, TA-015, and AEC Chromogen, TA-002-HAC, Lab Vision Corporation, USA). During this step, the tissues were washed with PBS after the signal was visualized by light microscopy.

The tissues, counterstained with Mayer's hematoxylin, were washed with PBS and distilled water and then covered with the appropriate mounting solution (Large Volume Vision Mount, TA-125-UG, Lab Vision Corporation, USA). The samples were analyzed, evaluated, and photographed under a Leica DM500 microscope (Leica DFC295). A histoscore was calculated based on the prevalence (0.1: <25%, 0.4: 26-50%, 0.6: 51-75%, 0.9: 76-100%) and severity (0: none, +0.5: very low, +1: low, +2: moderate, +3: severe) of immunoreactivity in staining. The histoscore is determined by multiplying prevalence by severity.

TUNEL study

Sections taken from paraffin blocks at a thickness of 4–6 µm were transferred to polylysine slides. Cells undergoing apoptosis were detected using the ApopTag Plus Peroxidase In Situ Apoptosis Detection Kit (Chemicon, cat no: S7101, USA) according to the manufacturer's instructions. Tissues deparaffinized with xylene were washed with phosphate-buffered saline (PBS) through a graded series of alcohols. The tissues were incubated with 0.05% proteinase K for 10 min and then with 3% hydrogen peroxide for 5 min to inhibit endogenous peroxidase activity. After washing with PBS, the tissues were incubated in Equilibration Buffer for 6 min, then in the working solution (70% Reaction Buffer+30% TdT Enzyme) for 60 min at 37 ˚C in a humidified chamber. The tissues were then placed in Stop/Wash Buffer for 10 min and processed with Anti-Digoxigenin-Peroxidase for 30 min. Apoptotic cells were visualized using diaminobenzidine (DAB) substrate (10).

The sections were counterstained with Harris hematoxylin and sealed with an appropriate sealing solution. The preparations were examined, evaluated, and photographed using a Leica DM500 microscope (Leica DFC295). In the assessment of TUNEL staining, nuclei stained blue with Harris hematoxylin were considered normal, while cells with brown nuclear staining were deemed apoptotic. At least 500 normal and apoptotic cells were counted in randomly selected areas at 10× magnification. The apoptotic index (AI) was calculated as the ratio of apoptotic cells to the total number of cells (normal plus apoptotic), and statistical analysis was performed.

Statistical analyses

SPSS 22.0 was used to analyze all data collected in this study. Numerical data were presented as median (minimum-maximum). The Shapiro-Wilk test was employed to assess whether the variables were normally distributed. The Kruskal-Wallis test was used for overall comparisons among more than two groups. Post-hoc Dunn's test was used to follow up on the Kruskal-Wallis test for comparisons between paired groups. A $P<0.05$ was considered statistically significant.

Results

Biochemical results

Serum total oxidant status (TOS) levels

In the biochemical study evaluating serum TOS levels across all groups, no statistically significant difference was observed between the Sham and DEX groups (P=0.805 and P=0.840, respectively). However, a statistically significant increase in TOS levels was observed in the I/R group (P=0.011). Additionally, a statistically significant decrease in TOS levels was observed in the I/R+DEX group compared to the I/R group (P=0.001)(Table 1).

Serum total antioxidant status (TAS) levels

In the biochemical study assessing serum TAS levels across all groups, no statistically significant difference was observed between the Sham and DEX groups (P=0.987, P=0.730, respectively) compared with the control group. However, a significant decrease in TAS levels was observed in the I/R group (p=0.007). When compared with the I/R group, there was a significant increase in TAS levels in the I/R+DEX group (P=0.001)(Table 1).

Serum TRPM2 levels

In serum, TRPM2 levels across all groups showed no statistically significant differences between the Sham and DEX groups (P=0.699, P=0.198, respectively) compared with the control group. In contrast, a significant increase in TRPM2 levels was observed in the I/R group (P=0.001). Compared to the I/R group, a significant decrease in TRPM2 levels was observed in the I/R+DEX group (P=0.014)(Table 1).

Serum TRPA1 levels

The biochemical study evaluating serum TRPA1 levels across all groups showed no statistically significant difference between the Sham and DEX groups (P=0.306, P=0.345, respectively) compared with the control group. However, a significant increase in TRPA1 levels was observed in the I/R group (P=0.001). Additionally, there was a significant decrease in TRPA1 levels in the I/R+DEX group compared to the I/R group (P=0.004)(Table 2).

Table 1. Serum total oxidant status (TOS) and total antioxidant status (TAS) levels of rats

	TOS (pg/ml)	TAS (U/ml)
	Median (min-max)	Median (min-max)
Control	54,82 (48,12-62,35)	5,35 (4,03-7,30)
Sham	55,33 (40,05-62,01)	5,59 (4,25-6,32)
DEX	55,62 (42,39-65,21)	5,21 (3,85-6,52)
I/R	121,91 (112,31-125,42) [a]	1,04 (0,39-1,23) [a]
I/R+DEX	52,54 (46,47-61,02) [b]	5,27 (4,33-7,02) [b]
p*	0.006	0.007

Values are given as median and min-max
[a] Compared to the Control group,
[b] Compared with the IR group, (P<0.05)
* Kruskal-Wallis
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion

Table 2. Serum TRPM2 and TRPA1 levels of rats

	TRPM2 (ng/ml)	TRPA1 (pg/ml)
	Median (min-max)	Median (min-max)
Control	34,56 (25,52-45,62)	126,89 (113,47-148,32)
Sham	36,89 (27,89-51,02)	148,92 (124,63-157,85)
DEX	45,80 (31,23-57,63)	148,76 (125,31-169,45)
I/R	148,45 (123,45-174,32) [a]	376,37 (299,46-403,62) [a]
I/R+DEX	39,97 (32,47-54,62) [b]	141,93 (113,04-177,42) [b]
p[*]	0.009	0.006

Values are given as median and min-max
[a] Compared to the Control group,
[b] Compared with the IR group, (P<0.05)
[*] Kruskal-Wallis
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion; TRPM2: Transient receptor potential melastatin 2; TRPA1: Transient receptor potential ankyrin 1

Table 3. TRPM2 and TRPA1 immunoreactivity histoscore of rats

	TRPM2	TRPA1
	Median (min-max)	Median (min-max)
Control	0,30 (0,20-0,45)	0,35 (0,20-0,45)
Sham	0,40 (0,10-0,60)	0,30 (0,10-0,45)
DEX	0,30 (0,20-0,40)	0,20 (0,10-0,60)
I/R	0,85 (0,45-1,80) [a]	0,90 (0,60-1,20) [a]
I/R+DEX	0,35 (0,10-0,45) [b]	0,30 (0,10-0,45) [b]
p[*]	0.011	0.004

Values are given as median and min-max
[a] Compared to the Control group,
[b] Compared with the IR group, (P<0.05)
[*] Kruskal-Wallis
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion; TRPM2: Transient receptor potential melastatin 2; TRPA1: Transient receptor potential ankyrin 1

Immunohistochemical results

TRPM2 immunoreactivity

Immunohistochemical staining for TRPM2 immunoreactivity was examined using light microscopy, and TRPM2 immunoreactivity was observed in tubule cells (black arrow) in kidney tissue (Figure 1).

In the immunohistochemical study conducted to evaluate TRPM2 immunoreactivity in kidney tissue across all groups, no statistically significant difference was observed in TRPM2 immunoreactivity between the Sham (Figure 1b) and DEX (Figure 1c) groups (P=0.984, P=0.573, respectively) compared to the control group (Figure 1a). However, a statistically significant increase in TRPM2 immunoreactivity was noted in the I/R4 (Figure 1d) (p=0.011). Compared to the I/R group, a significant decrease in TRPM2 immunoreactivity was observed in the I/R+DEX group (Figure 1e)(p=0.004)(Table 3).

TRPA1 immunoreactivity

Immunohistochemical staining for TRPA1 immunoreactivity was examined under light microscopy, and TRPA1 immunoreactivity was observed in tubule cells (black arrow) in kidney tissue.

The immunohistochemical study evaluating TRPA1 immunoreactivity in renal tissue across all groups showed no statistically significant difference in TRPA1 immunoreactivity between the Sham (Figure 2b) and DEX (Figure 2c) groups (p=0.783, p=0.550, respectively) compared with the control group (Figure 2a). In contrast, no statistically significant difference was observed in group I/R (Figure 2d). A statistically significant increase in TRPA1 immunoreactivity was observed in the I/R group (Figure 14) (p=0.018). Compared to the I/R group, a statistically significant decrease in TRPA1 immunoreactivity was seen in the I/R+DEX group (Figure 2e)(p=0.002)(Table 3).

TUNEL results

As a result of TUNEL staining performed to identify apoptotic cells under light microscopy, TUNEL positivity was observed in tubular cells (black arrow) in kidney tissue.

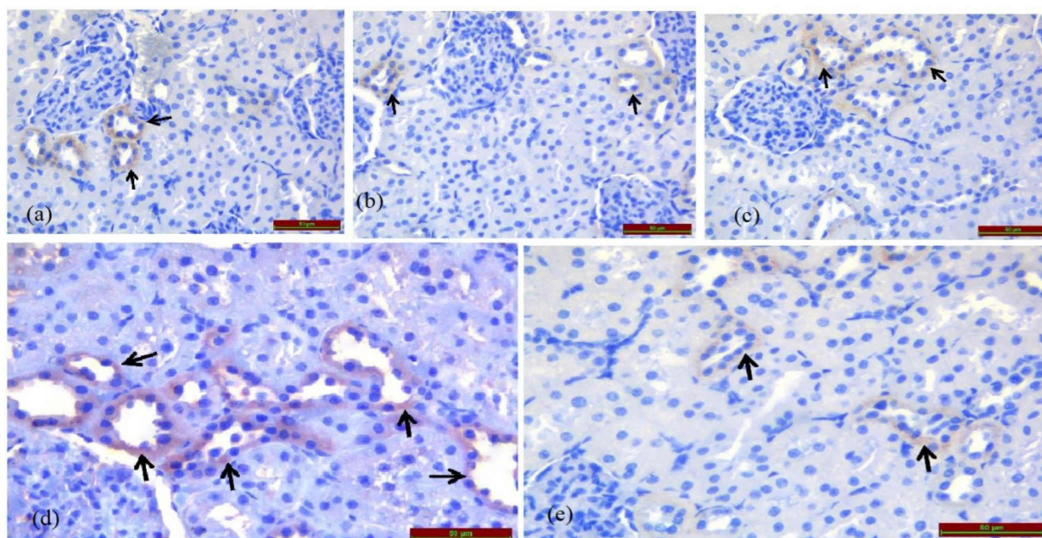

Figure 1. TRPM2 immunoreactivity in rat kidney tissue (→)
a) TRPM2 immunoreactivity in the kidney tissue of the control group, b) TRPM2 immunoreactivity in the kidney tissue of the sham group, c) TRPM2 immunoreactivity in the kidney tissue of the DEX group, d) TRPM2 immunoreactivity in the kidney tissue of the I/R group, e) TRPM2 immunoreactivity in the kidney tissue of the I/R+DEX group
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion

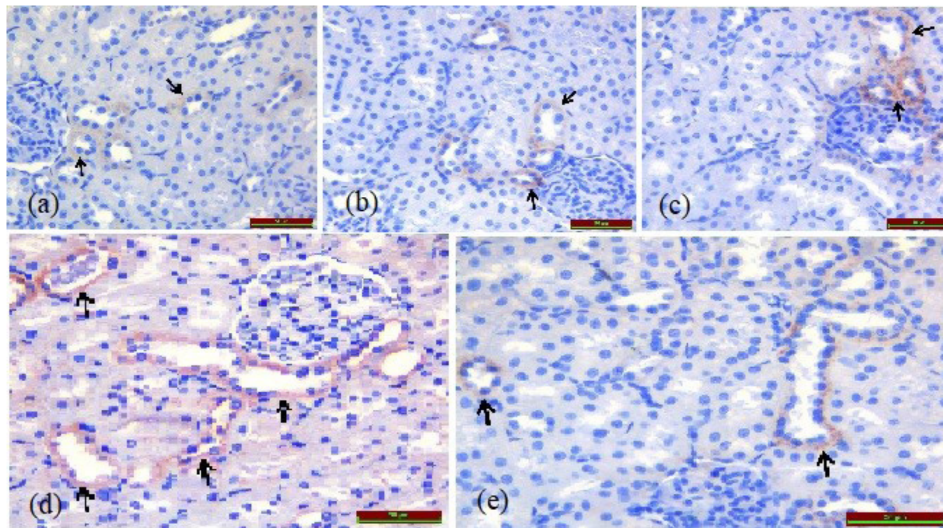

Figure 2. TRPA1 immunoreactivity in kidney tissue of rats (→)
a) TRPA1 immunoreactivity in the kidney tissue of the control group, b) TRPA1 immunoreactivity in the kidney tissue of the sham group, c) TRPA1 immunoreactivity in the kidney tissue of the DEX group, d) TRPA1 immunoreactivity in the kidney tissue of the I/R group, e) TRPA1 immunoreactivity in the kidney tissue of the I/R+DEX group
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion

In TUNEL staining used to evaluate apoptotic cells in the kidney tissue from all groups, no statistically significant difference was found in TUNEL positivity in the Sham (Figure 3b) and DEX (Figure 3c) groups (p=0.906, p=0.790, respectively) compared to the control group (Figure 3a), whereas a significant increase in TUNEL positivity was observed in the I/R group (Figure 3d)(p=0.006). When compared to the I/R group, the I/R+DEX group (Figure 3e) showed a significant decrease in TUNEL positivity (p=0.003)(Table 4).

Table 4. The apoptotic index to use for the evaluation of kidney tissue of all groups

	Apoptotic Index (%) Median (min-max)
Control	3,00 (1,00-4,00)
Sham	2,00 (2,00-5,00)
DEX	3,00 (1,00-3,00)
I/R	9,00 (6,00-14,00)[a]
I/R+DEX	2,50 (1,00-5,00)[b]
p[*]	0.006

Values are given as median and min-max
[a] Compared to the Control group, [b] Compared with the IR group, ($P<0.05$)
[*] Kruskal-Wallis
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion

Discussion

This study provides strong evidence that dexmedetomidine (DEX) protects against renal ischemia/reperfusion (I/R) injury by reducing oxidative stress and inhibiting redox-sensitive transient receptor potential (TRP) channels, specifically TRPM2 and TRPA1. To

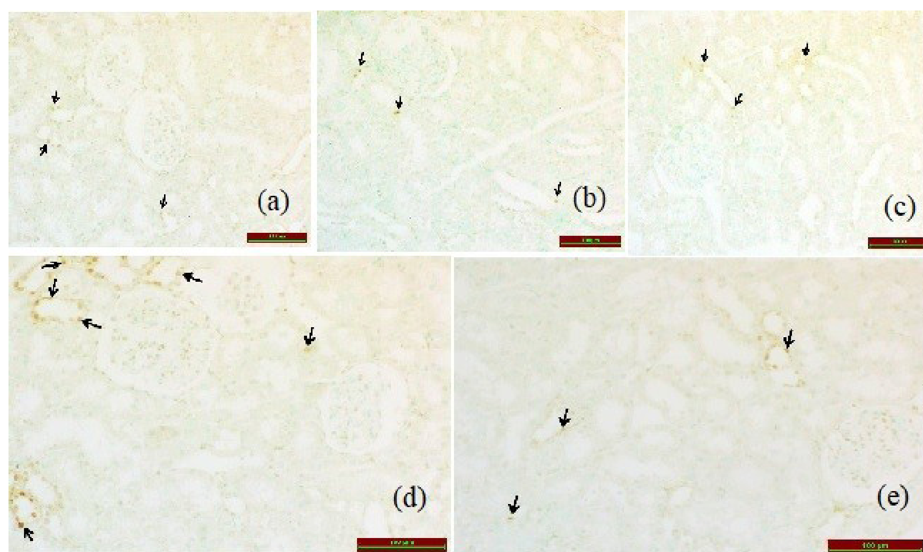

Figure 3. TUNEL-positive cells in rat kidney tissue (→)
a) TUNEL-positive cells in the kidney tissue of the Control group, b) TUNEL-positive cells in the kidney tissue of the Sham group, c) TUNEL-positive cells in the kidney tissue of the DEX group, d) TUNEL-positive cells in the kidney tissue of the I/R group, e) TUNEL-positive cells in the kidney tissue of the I/R+DEX group
DEX: Dexmedetomidine; I/R: Ischemia and reperfusion

our knowledge, it is one of the few experimental studies directly showing DEX's ability to lower TRPM2 and TRPA1 expression in renal tissue and serum, supported by consistent biochemical, immunohistochemical, and apoptotic indicators. We investigated the effect of DEX, which is increasingly used in anesthesiology and intensive care, on renal I/R injury and Redox-TRP channels. We found that DEX decreased serum TOS levels, increased TAS levels, reduced the Apoptotic Index, and lowered the expression of redox-TRP channels (TRPM2 and TRPA1) in both kidney tissue and serum.

Renal I/R injury remains a leading cause of acute kidney injury (AKI), associated with high morbidity and mortality, especially in perioperative and intensive care settings. The mechanisms behind renal I/R damage involve a complex interplay of oxidative stress, inflammation, and apoptosis, with redox-TRP channels increasingly recognized as key mediators of these harmful processes. Organ dysfunction after renal ischemia-reperfusion (I/R) injury typically involves increased microvascular permeability, interstitial edema, impaired vasoregulation, inflammatory cell infiltration, parenchymal cell dysfunction, and necrosis (11). An association between dexmedetomidine and a lower incidence of AKI has been shown (11, 12); however, how dexmedetomidine provides renal protection remains unclear. Dexmedetomidine likely exerts its renoprotective effects through combined sympatholytic, anti-inflammatory, and cytoprotective properties (13, 14). Additionally, it has been shown to decrease sympathetic-mediated presynaptic norepinephrine release in the kidney, reducing stress-induced increases in circulating norepinephrine (15). Our findings support previous research showing that TRPM2 and TRPA1 are up-regulated in response to oxidative stress and play roles in cellular injury pathways during renal I/R events. Renal function parameters (creatinine, BUN) were not measured in this study, which limits direct functional correlation. Future studies will incorporate these parameters to better evaluate the impact of DEX on renal function.

Dexmedetomidine affects multiple pathways involving G protein-coupled receptors. Alpha-2 adrenoreceptors activate protein kinase C and produce inositol triphosphate in renal distal convoluted tubule cells. This is important for ischemic preconditioning (16). Dexmedetomidine has also been shown to increase glomerular filtration rate and filtration fraction by decreasing renal vascular resistance, helping to prevent histopathological changes caused by potential ischemia (17). These findings support the idea that DEX protects against I/R-induced renal damage. In our model, I/R significantly increased total oxidant status (TOS), TRPM2 and TRPA1 expression, and apoptotic index in renal tissue, while decreasing total antioxidant status (TAS). Importantly, administering DEX at the start of reperfusion markedly reversed these changes. DEX significantly lowered TOS and the apoptotic index, restored TAS levels, and significantly suppressed TRPM2 and TRPA1 both at the protein expression level and in tissue immunoreactivity. When interpreting the experimental dose of dexmedetomidine (100 μg/kg), interspecies pharmacokinetic differences must be considered. Rodents metabolize alpha-2 agonists more rapidly than humans, owing to higher hepatic microsomal activity and greater basal metabolic rate. Therefore, doses used in rat I/R models are typically several-fold higher than those used clinically. When converted using standard allometric scaling methods, the 100 μg/kg intraperitoneal dose corresponds to an approximate human-equivalent dose (HED) of ~16 μg/kg, which remains within the pharmacologically relevant range reported for perioperative sedation and organ-protective experimental studies. Nonetheless, differences in receptor density, distribution, and drug clearance between species may affect the translational applicability, and future studies evaluating clinically comparable infusion protocols are warranted. Although 100 μg/kg DEX is widely used in experimental renal I/R models, the absence of a dose–response analysis represents a limitation. Future studies should compare multiple dosing regimens to define dose-dependent effects.

Redox-TRP channels are activated during I/R. TRPM2 is expressed in the kidney and can be activated by various molecules, including hydrogen peroxide, calcium, and cyclic adenosine diphosphate ribose (cADPR), which is produced during acute kidney injury (18). TRPM2 is primarily located in renal proximal tubule epithelial cells, and studies in chimeric mice have shown that the effects of TRPM2 depend on its expression in parenchymal cells rather than hematopoietic cells (19). In a renal I/R injury model, TRPM2 knockout mice exhibited better preservation of renal function, less histological damage, and increased resistance to ischemic injury by suppressing proapoptotic pathways. It has been demonstrated that DEX suppresses the TRPM2 and TRPV1 channels in neuronal tissue, potentially reducing damage. In our study, DEX administration significantly attenuated TRPM2 expression, supporting the hypothesis that DEX may exert its nephroprotective effects, at least in part, by inhibiting TRPM2.

TRPA1, although initially identified in nociceptive neurons, is also present in non-neuronal tissues, including renal tubular epithelium. Its role in kidney injury remains debated: some studies indicate pro-inflammatory effects via ROS sensing, whereas others suggest it may have protective effects under certain pathological conditions. The role of TRPA1 in tissue inflammation and damage remains a topic of ongoing debate. Recent research has shown that TRPA1 is expressed in various non-neuronal cells, including renal tubular cells (20). Activation of TRPA1 in these cells could exacerbate the inflammatory response (21). However, two animal studies suggest that TRPA1 may protect against kidney damage induced by sepsis or angiotensin II (22, 23). Conversely, several studies highlight TRPA1's antioxidant, anti-inflammatory, and organ-protective properties (24, 25). Research on TRPA1 and acute kidney injury (AKI) remains limited. Wu *et al.* reported that high TRPA1 levels in renal tubules could be a risk factor for tubular damage in AKI patients. Elevated TRPA1 in tubules was associated with more severe damage and worse renal outcomes after AKI, proposing it as a potential therapeutic target (21). In our study, DEX suppressed TRPA1 expression. DEX inhibits all redox-TRP channels, potentially reducing I/R injury. Our data revealed a significant increase in TRPA1 expression after I/R, which DEX effectively suppressed. This indicates that TRPA1 may act as a pro-inflammatory mediator during acute renal I/R injury, and DEX's capacity to reduce its expression may help explain some of its renoprotective effects. Although several studies have reported a protective role for TRPA1 activation in certain pathological contexts, particularly in models of sepsis or angiotensin II–mediated

injury, our findings are more consistent with models demonstrating that TRPA1 exacerbates tubular injury through its ROS-sensing properties. TRPA1 is activated by reactive aldehydes and oxidative by-products generated during ischemia and reperfusion, triggering intracellular calcium influx and pro-inflammatory signaling cascades. The apparent discrepancies across studies likely reflect differences in the underlying injury type (ischemia-reperfusion vs. inflammatory or metabolic injury), the duration and severity of the insult, and tissue-specific patterns of TRPA1 expression. In the acute I/R setting evaluated here, increased TRPA1 expression appears detrimental, and its suppression by DEX aligns mechanistically with the observed reduction in oxidative stress and apoptosis. The consistency of our findings across biochemical, histological, and immunohistochemical assessments underscores the robustness of our results. The reduction of TUNEL-positive cells with DEX further highlights its anti-apoptotic potential, likely through suppression of mitochondrial ROS production and subsequent caspase inhibition.

Our study's strength lies in its comprehensive analysis of TRPM2 and TRPA1 at both systemic (serum) and local (renal tissue) levels, along with strong histopathological correlations. This indicates a new molecular mechanism for its renoprotective effects. Considering the high incidence of AKI in surgical and critical care settings and the lack of targeted drug treatments, these findings could have a significant clinical impact. DEX, already widely used for sedation, might offer dual benefits by reducing renal oxidative damage. Targeting redox-TRP channels, particularly TRPM2 and TRPA1, presents a promising therapeutic strategy. But the lack of western blot or RT-PCR verification is a methodological limitation and emphasizes the need for these confirmatory techniques in future work. Future research should focus on evaluating selective TRPM2/TRPA1 inhibitors combined with DEX and exploring their potential in other organs affected by I/R injury.

Conclusion

The experimental renal I/R model increases TRPM2 and TRPA1 expression, promotes apoptosis, and raises TOS levels in tissue and serum while decreasing TAS levels. DEX reduces cellular oxidation and apoptosis, thereby strengthening protective effects. These findings reveal a new mechanism of action for DEX and support its potential use not only as a sedative but also as a therapeutic modulator of redox-sensitive ion channels to prevent AKI. We believe that TRPM2 and TRPA1 may serve as important biomarkers in the pathophysiology of renal ischemia/reperfusion, and further studies with redox-TRP channel blockers and/or inhibitors, such as DEX, could potentially be applied clinically in cases of acute kidney injury.

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Availability of Data and Material

All the data are given in the article.

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Authors' Contributions

A U and E B designed the experiments; E B, O D, and A U performed the experiments and collected data; T K, A T, and G A discussed the results and strategy; T K and E B supervised, directed, and managed the study; A U, T K, O D, A T, G A, and E B approved the final version for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Declaration

We did not use any AI tools or technologies in preparing this manuscript.

References

1. Ren M, Sun LL, Tu YC, Feng L, Yao LJ. Redox TRPs in ıschemia-reperfusion ınjury and their pharmacological value. Front Biosci (Landmark Ed) 2024; 29: 170.
2. Wang X, Lei XG, Wang J. Malondialdehyde regulates glucose-stimulated insulin secretion in murine islets via TCF7L2-dependent Wnt signaling pathway. Mol Cell Endocrinol 2014; 382: 8-16.
3. Maier CM, Sun GH, Kunis DM, Giffard RG, Steinberg GK. Neuroprotection by the N-methyl-D-aspartate receptor antagonist CGP 40116: *In vivo* and *in vitro* studies. J Neurochem 1995; 65: 652-659.
4. Kocoglu H, Karaaslan K, Gonca E, Bozdogan O, Gulcu N. Preconditioning effects of dexmedetomidine on myocardial ischemia/reperfusion injury in rats. Curr Ther Res Clin Exp 2008; 69: 150-158.
5. Hoffman WE, Kochs E, Werner C, Thomas C, Albrecht RF. Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat. Reversal by the alpha 2-adrenergic antagonist atipamezole. Anesthesiology 1991; 75: 328-332.
6. Kocoglu H, Ozturk H, Ozturk H, Yilmaz F, Gulcu N. Effect of dexmedetomidine on ischemia-reperfusion injury in rat kidney: A histopathologic study. Ren Fail 2009; 31: 41-70.
7. Crowther JR. The ELISA guidebook. Methods Mol Biol 2000; 149: 1-413.
8. Ramos-Vara JA. Technical aspects of immunohistochemistry. Vet Pathol 2005; 42: 405-426.
9. Gavrieli Y, Sherman Y, Ben-Sasson SA. Identification of programmed cell death *in situ* via specific labeling of nuclear DNA fragmentation. J Cell Biol 1992; 119: 493-501.
10. Caron A, Desrosiers RR, Béliveau R. Kidney ischemia-reperfusion regulates expression and distribution of tubulin subunits, beta-actin and rho GTPases in proximal tubules. Arch Biochem Biophys 2004; 431: 31-46.
11. Shiva N, Sharma N, Kulkarni YA, Mulay SR, Gaikwad AB. Renal ischemia/reperfusion injury: An insight on *in vitro* and *in vivo* models. Life Sci 2020; 256: 117860.
12. Ishii M, Shimizu S, Hara Y, Hagiwara T, Miyazaki A, Mori Y, *et al.* Intracellular-produced hydroxyl radical mediates H2O2-induced Ca^{2+} influx and cell death in rat beta-cell line RIN-5F. Cell Calcium 2006; 39: 487-494.
13. Bao N, Tang B. Organ-protective effects and the underlying mechanism of dexmedetomidine. Mediators Inflamm 2020; 2020: 6136105.
14. Zhao S, Wu W, Lin X, Shen M, Yang Z, Yu S, *et al.* Protective effects of dexmedetomidine in vital organ injury: Crucial roles of autophagy. Cell Mol Biol Lett 2022; 27: 34.
15. Taoda M, Adachi YU, Uchihashi Y, Watanabe K, Satoh T, Vizi ES. Effect of dexmedetomidine on the release of [3H]-noradrenaline from rat kidney cortex slices: Characterization of alpha2-adrenoceptor. Neurochem Int 2001; 38: 317–322.

16. Curtis FG, Vianna PT, Viero RM, Fiorio PM, Silva LM, Braz JRC, *et al*. Dexmedetomidine and S+-ketamine in ischemia and reperfusion injury in the rat kidney. Acta Cir Bras 2011; 26: 202-206.
17. Marangoni MA, Hausch A, Vianna PT, Braz JRC, Viero RM, Castiglia YMM. Renal function and histology after acute hemorrhage in rats under dexmedetomidine action. Acta Cir Bras 2007; 22: 291-298.
18. Eraslan E, Tanyeli A, Polat E, Polat E. 8-Br-cADPR, a TRPM2 ion channel antagonist, inhibits renal ischemia-reperfusion injury. J Cell Physiol 2019; 234: 4572-4581.
19. Gao G, Wang W, Tadagavadi RK, Briley NE, Love MI, Miller BA, *et al*. TRPM2 mediates ischemic kidney injury and oxidant stress through RAC1. J Clin Invest 2014; 124: 4989-5001.
20. Dembla S, Hasan N, Becker A, Beck A, Philipp SE. Transient receptor potential a1 channels regulate epithelial cell barriers formed by mdck cells. FEBS Lett 2016; 590: 1509-1520.
21. Wu CK, Wu CL, Su TC, Kou YR, Kor CT, Lee TS, *et al*. Renal tubular TRPA1 as a risk factor for recovery of renal function from acute tubular necrosis. J Clin Med 2019; 8: 2187.
22. Zhu J, Zhang S, Geng Y, Song Y. Transient receptor potential ankyrin 1 protects against sepsis-induced kidney injury by modulating mitochondrial biogenesis and mitophagy. Am J Transl Res 2018; 10: 4163–4172.
23. Ma S, Zhang Y, He K, Wang P, Wang DH. Knockout of trpa1 exacerbates angiotensin ii-induced kidney injury. Am J Physiol Renal Physiol 2019; 317: F623–F631.
24. Kun J, Szitter I, Kemeny A, Perkecz A, Kereskai L, Pohoczky K, *et al*. Upregulation of the transient receptor potential ankyrin 1 ion channel in the inflamed human and mouse colon and its protective roles. PLoS One 2014; 9: 108164.
25. Lowin T, Apitz M, Anders S, Straub RH. Anti-inflammatory effects of n-acylethanolamines in rheumatoid arthritis synovial cells are mediated by trpv1 and trpa1 in a cox-2 dependent manner. Arthritis Res Ther 2015; 17: 321.