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Original research paper

Modulatory effects of perindopril on cisplatin-induced nephrotoxicity in mice: Implication of inflammatory cytokines and caspase-3 mediated apoptosis

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Cisplatin-induced nephrotoxicity limits its anticancer effectiveness, thus this study's aim was to assess the potential modulatory effect of perindopril on cisplatin-induced nephrotoxicity and to elucidate the possible underlying mechanisms. Renal dysfunction was induced in mice by a single injection of cisplatin (10 mg kg^{-1}, *i.p.*) and perindopril was administered orally (2 mg kg^{-1}, once daily) for 5 days. Perindopril remarkably ameliorated cisplatin-induced perturbations in renal histology, renal levels of tumor necrosis factor-alpha, interleukin-6 and interleukin-10, apoptosis-regulating protein expressions (Bax and Bcl2), and partially normalized Bax to Bcl2 ratio and active caspase 3 protein expression. Conversely, perindopril had no significant effect on cisplatin-induced elevations in serum creatinine and urea, microalbuminuria, kidney to body weight ratio, lipid peroxidation marker, superoxide dismutase and catalase activities and reduced glutathione content. In conclusion, perindopril may be safely used with cisplatin in mice since it ameliorated cisplatin-induced histopathological changes, inflammation and apoptosis without affecting renal biomarkers or oxidative stress.

Keywords: perindopril, cisplatin, nephrotoxicity, oxidative stress, apoptosis, inflammation

Cisplatin is a chemotherapeutic drug clinically effective against various types of malignancies. However, due to frequent adverse effects including bone marrow suppression, neurotoxicity, ototoxicity, and notably nephrotoxicity, its clinical utility has been hampered (1). The major excretion route of cisplatin is renal. Cisplatin accumulates in the renal tissue resulting in necrosis of the proximal renal tubules and apoptosis in the distal nephron (2). About 30 %

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of patients receiving high-dose cisplatin have experienced severe renal dysfunction (3). Cisplatin has been reported to injure several renal structures including blood vessels, glomeruli, and most commonly the renal tubules (4). Clinical reports show that cisplatin--induced renal toxicity often results in acute renal failure, which is characterized by declines in renal blood flow within 3 hours of cisplatin administration and decreased glomerular filtration rate (5). Other complications, namely elevated levels of serum creatinine and blood urea nitrogen, have also been reported in both acute and chronic cisplatin-induced renal toxicity (6). Several experimental studies suggest a sequential injury pathway in cisplatin--induced renal toxicity, particularly conversion to toxic metabolites, induction of nuclear and mitochondrial DNA damage, oxidative stress and mitochondrial dysfunction, induction of inflammation and activation of apoptotic pathway (7, 8). Prevention of cisplatin-induced nephrotoxicity reduces complications and may allow administration of a higher dose of cisplatin with added therapeutic potential. Clinical approaches to improve cisplatin--induced-nephrotoxicity have been ongoing, however, there is no optimal protective agent. Therefore, it is pertinent to develop a therapy to limit the cisplatin-induced nephrotoxicity that might target one or more of cisplatin-nephrotoxic pathways (9). Many patients who are receiving cisplatin might be using additional drugs to control other diseases such as hypertension for which angiotensin-converting enzyme inhibitors (ACEIs) are the first-line choice. Studies on interactions between cisplatin and ACEIs drugs are limited.

Perindopril is an oral ACEI prodrug that results in decreased plasma angiotensin II level, decreased vasoconstriction, and decreased aldosterone secretion (10). Perindopril is approved for the treatment of hypertension, arterial stiffness, left ventricular hypertrophy, post-myocardial infarction and reduction of albuminuria in patients with hypertension and nephropathy or diabetes mellitus (10, 11). Accumulated evidence suggests the role of localized renin-angiotensin system (RAS) in the progression of different pathologies. RAS stimulation mediates oxidative and inflammatory damage, mostly *via* activation of NADPH oxidase and the inhibition of endothelial nitric oxide synthase (12, 13). Interestingly, interference with localized RAS in different animal models using ACEIs was shown to offer protective effects in the liver (14), respiratory tract (15), joints (16) and the brain (13). The aim of the present study was to examine the possible modulatory effects of perindopril on cisplatin-induced acute nephrotoxicity in mice and the potential mechanisms behind this modulation.

EXPERIMENTAL

Chemicals

Cisplatin and perindopril were purchased from Sigma-Aldrich (USA).

Animals

Male Swiss albino mice, weighing 25–30 g, were purchased and housed within the animal facility at Faculty of Pharmacy, Al-Azhar University. Animals care, treatment and sampling were executed in agree with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978).

Design of the work

Mice were randomly assigned to four groups (8 mice each) as follows: 1. Control group: injected *i.p.* with saline (0.1 mL per 20 g body mass) once daily for 5 consecutive days; 2. Perindopril group: mice treated orally with perindopril (2 mg kg^{-1}, once daily) for 5 consecutive days (17, 18); 3. Cisplatin group: mice injected *i.p.* with a single dose of cisplatin (10 mg kg^{-1}) (19, 20); 4. Cisplatin + perindopril group: mice treated with perindopril for 5 days starting 1 h before cisplatin (doses as above). The first day of drug treatment was considered day zero. On day 5, all animals were weighed, then euthanized and the serum samples were collected for the assessment of kidney functions. Urine samples were collected at end of experiment and centrifuged (2000 g at 4 °C for 15 min) after which the supernatant was used for the assessment of microalbuminuria. Both kidneys from each animal were collected and weighed to calculate relative kidney mass to body mass. Portions of the kidneys were rapidly stored at −80 °C until analyses were performed. Another portion of the kidney was placed immediately in 10 % neutral buffered formalin for histopathological and immunofluorescence examinations.

Evaluation of kidney status

Serum renal biomarkers and microalbuminuria. – Sera were carefully separated from fresh blood samples and used for determination of serum kidney function markers (creatinine and urea) using colorimetric diagnostic kits according to the manufacturer's instructions (Biodiagnostic Ltd., UK). In addition, microalbuminuria was measured according to the manufacturer's instructions (Biosystems, Spain).

Histopathological evaluation of kidney. – A portion of kidney was rinsed with ice-cold saline then embedded in 10 % neutral-buffered formalin for 48 h. Samples were dehydrated by alcohol, cleared by xylol, and finally embedded in paraffin blocks. Paraffin-embedded specimens were cut into sections of 4–6 microns thickness, placed on poly-lysine coated slides. Slides were deparaffinized, rehydrated with ethanol, rinsed in distilled water and stained with hematoxylin and eosin (H&E) before microscopical examination (Leica Imaging Systems, UK).

Determination of oxidative stress markers

Renal tissues were weighed and homogenized (1:10, *m*/*V*) in phosphate-buffered saline (pH 7.4), then centrifuged (2000 g at 4 °C) for 15 min and the supernatant was used to measure oxidative stress biomarkers. Renal content of malonaldehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) were evaluated in the whole tissue homogenate and normalized to the protein content in each sample using commercial kits (Bio-Diagnostics, Egypt).

*Measurement of renal tumor necrosis factor-alpha (TNF-**α**), interleukin-6 (IL-6) and interleukin-10 (IL-10)*

Supernatants of renal tissues homogenates were used to measure TNF-α using Mouse TNF-α ELISA Kit (Sigma-Aldrich Co, USA), IL-6 using mouse IL-6 ELISA kit (RayBiotech, Inc., USA) and IL-10 using mouse IL-10 ELISA kit (Cusabio Technology LLC, USA) according to the manufacturer's instructions.

Immunofluorescent assay of renal Bax, Bcl2 and active caspase 3 proteins

Immunofluorescent staining was performed to determine the differences in immunoreactivity intensity of Bax, Bcl2 and Caspase 3 proteins in renal tissues collected from mice allocated to different treatment groups. Briefly, tissue sections were deparaffinized in 100 % xylene and rehydrated through a graded ethanol series. Antigen retrieval was performed by incubating the tissue sections for 20 min in 0.01 mol L^{-1} sodium citrate buffer, pH 6.0, in a microwave oven. Briefly, the samples were initially boiled in a microwave at 800 W for 3 min, then for 7 min at 400 W to continue boiling. After cooling down for 30 min at room temperature (25 °C), the 10-min heating procedure was repeated with fresh buffer. Next, the sections were treated with blocking buffer [1 % horse serum in PBS] for 1 h. Tissue sections were incubated overnight at 4 °C in a humidified chamber with the primary antibodies; Bax (1: 250; Santa Cruz Biotechnology, USA), Bcl2 (1: 250; Santa Cruz Biotechnology), and Active Caspase 3 (1: 250; Santa Cruz Biotechnology). After washing, bound antibodies were detected by Texas Red labeled goat anti-mouse secondary antibodies (Thermo Fisher Scientific, USA). Nuclei were stained with DAPI and slides were mounted in Fluoromount G. The specificity of the immunoreaction was confirmed by incubation with PBS instead of the primary antibodies. The evaluation was performed by Nikon fluorescence microscope (Nikon eclipse 90i with a DS-U3 imaging system, Nikon Metrology, Inc., USA) under blue, green, and red channels. Fluorometric density analysis was performed using ImageJ/NIH software (National Institute of Health, USA). Fluorometric intensities of nine microscopic fields with exact areas and same resolutions were measured for each tissue section. Data represented as mean ± SD (n = 8).

Statistical analysis

Data were presented as means ± standard deviation (SD). Graphpad prism V5 (Graphpad Prism Software Inc., USA) was used to perform the one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test. Statistical significance was accepted at $p < 0.05$.

RESULTS AND DISCUSSION

Effect of perindopril on kidney status

Cisplatin caused significant elevations in serum creatinine, urea and microalbuminuria by 4.6, 10.8 and 2.3 folds of control group respectively (Table I). Administration of perindopril in cisplatin-treated mice had no significant effect on renal dysfunction induced by cisplatin since the levels of serum creatinine, urea and microalbuminuria were still significantly elevated at 4.3, 11 and 2.7 folds of control group respectively (Table I).

The kidney mass to body mass ratio was significantly increased by cisplatin to 1.3 fold of the control group (Table I). Perindopril was unable to correct cisplatin-induced elevation in the ratio of kidney mass to body mass.

In addition to kidney mass to body mass ratio, histopathological examination using H&E stain revealed normocellular glomeruli and patent tubular lumen lined by cuboidal epithelium normal kidney architecture in control and perindopril groups (Fig. 1). In the cisplatin group, there was marked vacuolar alteration of the tubular epithelium with occasional tubular cystic dilatation filled with hyaline casts (Fig. 1). Cotreatment with

Table I. Effect of perindopril on cisplatin-induced changes in renal biomarkers

	Control	Perin	Cis	Cis + Perin
Serum creatinine (mg dL^{-1})	0.17 ± 0.05	0.13 ± 0.04	0.78 ± 0.20*	0.73 ± 0.12[a]
Serum urea (mg dL^{-1})	26.33 ± 4.18	25 ± 3.74	284.33 ± 33.60*	290 ± 14.14[a]
Microalbuminuria (mg L^{-1})	300 ± 53.57	221.67 ± 23.17	700 ± 82.28*	800 ± 78.99[a]
% KM/BM	1.20 ± 0.12	1.21 ± 0.10	1.58 ± 0.20*	1.66 ± 0.23[a]

Renal dysfunction was induced in mice by a single cisplatin (Cis) injection (10 mg kg^{-1}, *i.p.*). Perindopril (Perin) was administered orally (2 mg kg^{-1}, once daily) for 5 days starting 1 h before Cis injection; and then serum creatinine, serum urea, microalbuminuria and percentage of kidney mass from total body mass (% KM/BM) were measured. Data are represented as mean ± SD (n = 8); [a] significant difference from the control group ($p < 0.05$); using ANOVA followed by Tukey's *post hoc* test.

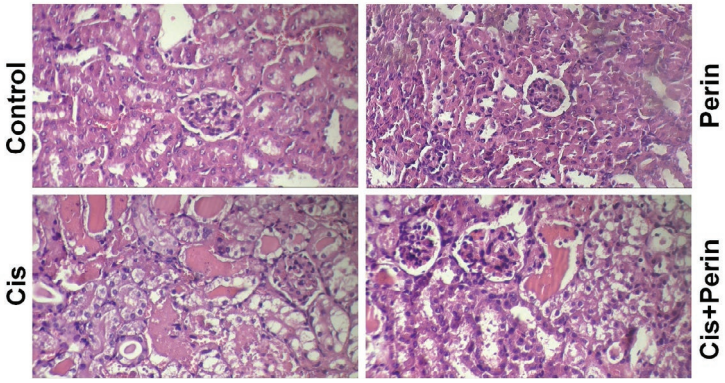

Fig. 1. Effect of perindopril on cisplatin-induced changes in kidney histopathology. Renal dysfunction was induced in mice by a single cisplatin (Cis) injection (10 mg kg^{-1}, *i.p.*). Perindopril (Perin) was administered orally (2 mg kg^{-1}, once daily) for 5 days starting 1 h before Cis injection. H&E stain of renal tissue sections revealed normocellular glomeruli and patent tubular lumen lined by cuboidal epithelium normal kidney architecture in control and Perin groups. In the Cis group, marked vacuolar alteration of the tubular epithelium with occasional tubular cystic dilatation filled with hyaline casts. Cis+Perin group showed mild glomerular hypercellularity, vacuolar alteration of the tubular epithelium with occasional hyaline casts and scattered interstitial mononuclear inflammatory cell infiltrate.

perindopril caused regression of these structural changes as shown by mild glomerular hypercellularity, vacuolar alteration of the tubular epithelium with occasional hyaline casts and scattered interstitial mononuclear inflammatory cell infiltrate (Fig. 1).

Based on these results, cisplatin-induced acute nephrotoxicity was documented in this study via elevation of serum creatinine and urea in addition to microalbuminuria, histopathological perturbations of kidney tissues and kidney hypertrophy as indicated by the increase in kidney mass to body mass ratio. Interestingly, perindopril administration for 5 days had partially ameliorated cisplatin-induced nephrotoxic effect which was documented in histological analysis of renal tissue sections. Conversely, using perindopril for

a longer period (14 days *vs*. 5 days in our study) in a rat model of acute cisplatin-induced nephrotoxicity showed protective effect of perindopril on cisplatin-induced serum renal biomarkers and kidney hypertrophy (21). Collectively, it is plausible that perindopril had no deteriorating effect on cisplatin-induced nephrotoxicity and it may require more time to reflect the improvement in renal functions.

Effect of perindopril on oxidative stress

Experimental evidence has indicated the basic role of oxidative stress in the pathogenesis of cisplatin-induced nephrotoxicity (22, 23). In our study, cisplatin had induced oxidative stress in renal tissue which is manifested by increased level of lipid peroxidation marker (MDA) to 2.0 folds of control group (Fig. 2d) and attenuation of both enzymatic (SOD and CAT) and non-enzymatic antioxidant defense (GSH) to 0.7, 0.5 and 0.5 folds of control group respectively (Fig. 2a-c). Coadministration of perindopril with cisplatin resulted in non-significant changes in these oxidative stress markers. Conversely, previous studies showed antioxidant activities for perindopril (21, 24). This might be due difference in disease model and treatment.

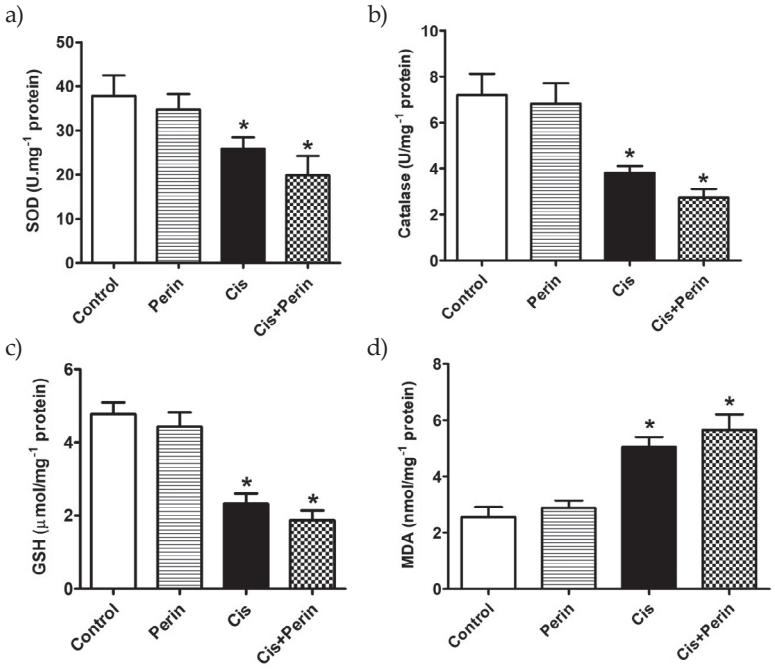

Fig. 2. Effect of perindopril on cisplatin-induced renal oxidative stress. Renal dysfunction was induced in mice by a single cisplatin (Cis) injection (10 mg kg^{-1}, *i.p.*). Perindopril (Perin) was administered orally (2 mg kg^{-1}, once daily) for 5 days starting 1 h before Cis injection. Renal tissue activity of: a) SOD and b) catalase in addition to c) GSH and d) MDA content were measured. Data represented as mean ± SD (n = 8). * indicates a significant difference from the control group ($p < 0.05$); using ANOVA followed by Tukey's *post hoc* test.

Effect of perindopril on inflammatory markers

In addition, induction of inflammation has been also implicated in cisplatin-induced renal tissue injury (1, 4, 8). The current work has demonstrated that cisplatin had significantly elevated proinflammatory cytokines TNF-α and IL-6 in renal tissue to 5.7 and 7.9 folds of control group respectively (Fig. 3a,b). Furthermore, cisplatin significantly decreased the renal level of the antiinflammatory cytokine IL-10 to 0.4 folds of control group (Fig. 3c). Treatment with perindopril ameliorated cisplatin-induced inflammatory pathway as indicated by the decrease in the levels of TNF-α and IL-6 to 2.3 and 3.6 folds respectively and the elevation of IL-10 to 1.6 folds of control group value. Perindopril treatment in control mice had no significant effect on these inflammatory cytokines.

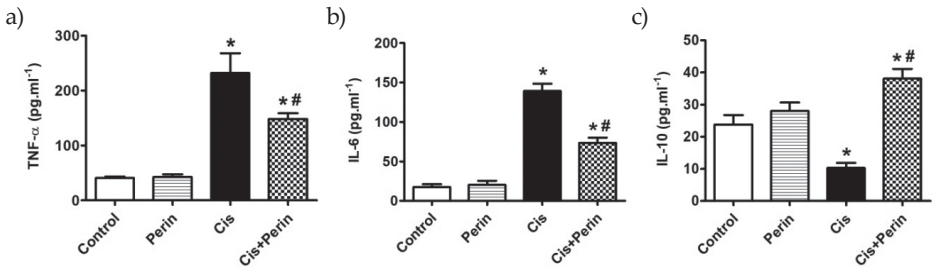

Fig. 3. Effect of perindopril on cisplatin-induced changes in renal levels of TNF-α, IL-6 and IL-10. Renal dysfunction was induced in mice by a single cisplatin (Cis) injection (10 mg kg^{-1}, *i.p.*). Perindopril (Perin) was administered orally (2 mg kg^{-1}, once daily) for 5 days starting 1 h before Cis injection; and then: a) TNF-α b) IL-6 and c) IL-10 were measured in renal tissue total homogenate. Data represented as mean ± SD (n = 8). *or # indicates a significant difference from control or Cis groups respectively ($p < 0.05$); using ANOVA followed by Tukey's *post hoc* test.

It is documented that the induction of oxidative stress could induce inflammation of somatic cells (25, 26). However, in our study, perindopril alleviated cisplatin-induced inflammation without affecting cisplatin-induced oxidative stress, suggesting that the antiinflammatory effect of perindopril is independent from its antioxidant effect.

Effect of perindopril on markers of apoptosis

Both inflammation and oxidative stress have been associated with caspase-dependent renal cellular apoptosis (25, 27–29). Our study indicated that cisplatin administration has significantly increased the expression of the proapoptotic Bax protein 4.8 folds of control group (Fig. 4a and 4c) and significantly decreased anti-apoptotic protein Bcl-2 level to 0.3-fold of control group (Fig. 4b and 4d) and hence, the Bax to Bcl2 ratio was significantly increased to 3.6 folds of control (Fig. 4e). Increased Bax to Bcl2 ratio may favor the release of cytochrome c and could have led to the significant increase in active caspase-3 protein expression in renal tissues (30–32), which was confirmed by our results whereas, cisplatin had induced a significant increase in the expression of active caspase 3 to 14.32 folds of control (Fig. 5a,b). These events could significantly contribute to renal cell death, which

was further confirmed by histopathological investigation, changes in renal to body mass ratio and reduced renal function.

Interestingly, coadministration of perindopril with cisplatin significantly has decreased the expression of Bax and caspase-3 proteins to 2.5 and 7.0 folds of control respectively and has increased the antiapoptotic protein Bcl2 to 0.4 folds of control and remarkably normalized BAX to Bcl2 ratio, highlighting its abatement on apoptotic activity and reinforcing its potential protective effect against cisplatin-induced renal injury.

It is worth mentioning that our study examined the potential interaction between cisplatin and perindopril in a murine model. Although both drugs are commonly used in

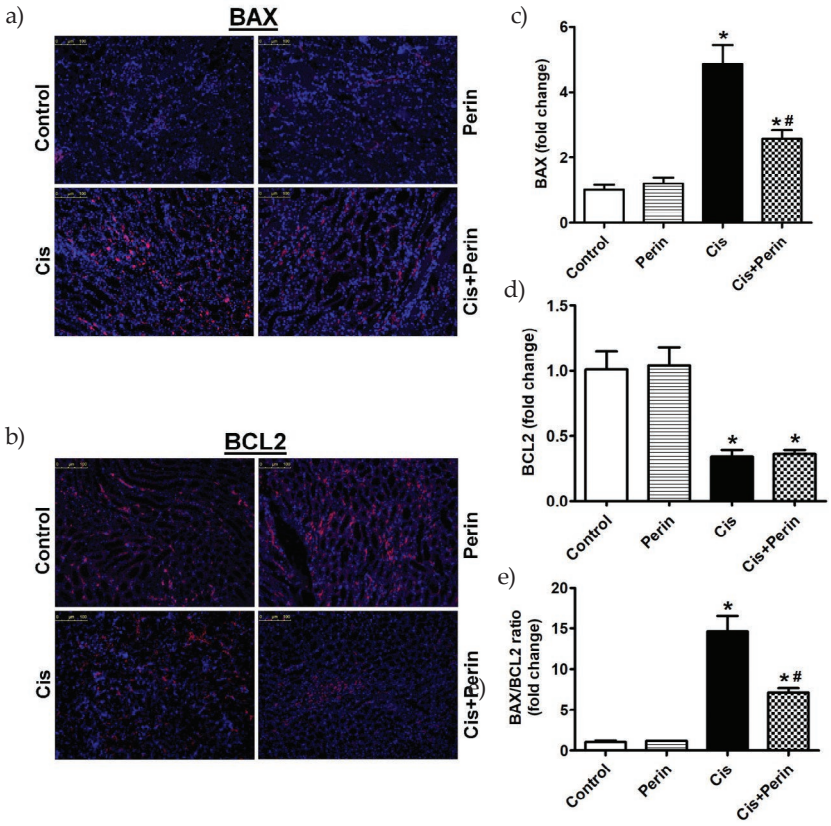

Fig. 4. Effect of perindopril on cisplatin-induced changes in the expression of renal BAX and BCL2 proteins. Renal dysfunction was induced in mice by a single cisplatin (Cis) injection (10 mg kg^{-1}, *i.p.*). Perindopril (Perin) was administered orally (2 mg kg^{-1}, once daily) for 5 days starting 1h before Cis injection; and then BAX and BCL2 were measured. a) representative BAX immunofluorescence images, b) representative BCL2 immunofluorescence images, c) BAX quantification, d) BCL2 quantification, e) ratio of BAX to BCL2. The fluorometric intensity of at least nine microscopic fields was measured for each tissue section. Data represented as mean ± SD ($n = 8$). *, # indicate a significant difference from control and Cis groups respectively ($p < 0.05$); using ANOVA followed by Tukey's *post hoc* test.

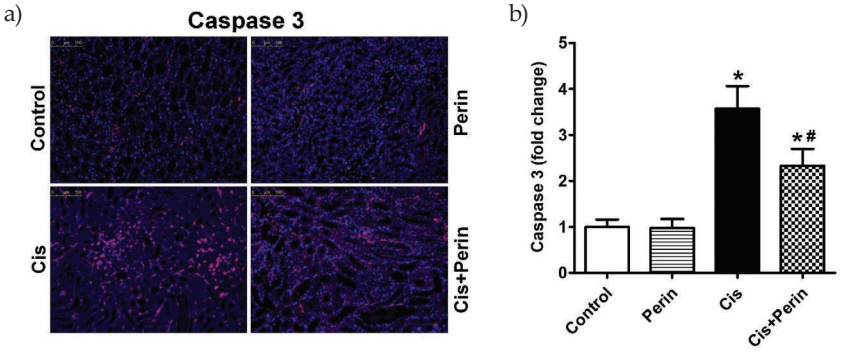

Fig. 5. Effect of perindopril on cisplatin-induced changes in renal caspase 3 protein expression. Renal dysfunction was induced in mice by a single cisplatin (Cis) injection (10 mg kg^{-1}, *i.p.*). Perindopril (Perin) was administered orally (2 mg kg^{-1}, once daily) for 5 days starting 1 h before Cis injection; and then Caspase 3 was measured. a) representative Caspase 3 immunofluorescence images, b) Caspase 3 quantification. Data represented as mean ± SD (n = 8). *, # indicates a significant difference from control and Cis groups respectively ($p < 0.05$); using ANOVA followed by Tukey's *post hoc* test.

clinical situations, only a single study in a different model has examined this interaction (21), possibly during our study timeframe. The underlying mechanism behind this interaction was partially elucidated in our study including the amelioration of cisplatin-induced inflammation and apoptosis of renal cells. However, oxidative stress was not affected by perindopril which is in contrast with the previously mentioned study (21). Further studies are required on this interaction using a different animal model and different dose levels for longer duration to gain more data.

CONCLUSIONS

Perindopril may be safely used with cisplatin in mice. Perindopril ameliorated cisplatin-induced acute renal injury via abrogation of cisplatin-induced inflammation in renal cells and apoptosis without affecting oxidative stress or renal biomarkers.

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Abbreviations. – ACEI, angiotensin-converting enzyme inhibitor; ANOVA, one-way analysis of variance; BAX, Bcl2 Associated X protein; Bcl2, B-cell lymphoma 2 protein; CAT, catalase; GSH, reduced glutathione; H&E, hematoxylin and eosin; IL-6, interleukin-6; IL-10, interleukin-10; MDA, malondialdehyde; RAS, renin-angiotensin system; SD, standard deviation; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha.

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