Sumatriptan ameliorates renal injury induced by cisplatin in mice

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A R T I C L E   I N F O

A B S T R A C T

Objective(s): Cisplatin (Cis) is an anticancer compound, which is used for the treatment of various cancers. Sumatriptan (Suma) is a selective agonist of 5-hydroxytryptamine 1B/1D (5HT1B/1D) receptor, which is prescribed for the management of migraine. It is well-established that Suma has anti-inflammatory and antioxidant properties. We have explored the protective effects of Suma in the mitigation of Cis-induced nephrotoxicity.

Materials and Methods: The mice received a single IP injection of Cis (20 mg/kg) on the first day of the experiment. Suma treatment (0.1 and 0.3 mg/kg/day, IP) was started on day 1 and continued for 3 consecutive days.

Results: Creatinine (Cr), blood urea nitrogen (BUN) and malondialdehyde (MDA) levels were elevated and glutathione peroxidase (GPx) as well as superoxide dismutase (SOD) activities were decreased in Cis-treated mice. Suma (more potently 0.3 mg/kg) reduced Cr, BUN and MDA levels and increased SOD and GPx levels. Suma also reduced the acute renal injury (tubular degeneration, tubular cells vacuolation, tubular necrosis and cast), which corresponded to kidney damage in Cis-treated mice.

Conclusion: These findings demonstrate that Suma mitigates Cis-induced renal injury by inhibition of oxidative stress and enhancing the antioxidant enzymes activities.

Introduction

Cisplatin (Cis) is an antineoplastic drug, which is used in the treatment of different cancers (1). Renal toxicity is the most important side effects of Cis-based chemotherapy, which limits the usage of this drug in clinic (2). The mechanism of nephrotoxicity induced by Cis is not completely understood. However, oxidative stress and lipid peroxidation have been implicated as contributing factors (3, 4). It is well-established that overgeneration of reactive oxygen species (ROS) increases malondialdehyde (MDA) and decreases the enzymes of antioxidant system such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in renal tissue, which are the major alterations in Cis-induced nephrotoxicity (5, 6). It has been reported that Cis increases the blood urea nitrogen (BUN) and creatinine (Cr) (7, 8). Therefore, there is a need to pursue a compound that can efficiently diminish Cis-induced nephrotoxicity to improve the chemotherapeutic efficacy of Cis.

Sumatriptan (Suma), a selective agonist of 5-hydroxytryptamine 1B/1D (5HT1B/1D) receptor, is a well-tolerated drug for the management of cluster headache and migraine. Suma has minor and transient adverse effects (9, 10). Recent studies have introduced some biological activities, including anti-inflammatory and antinociceptive effects for Suma (11, 12). Suma

induces direct antioxidant properties through scavenging the nitric oxide (NO) and ROS (13). It is well-established that Suma causes marked vasoconstrictor responses in kidney, which is followed by a secondary vasodilatation through release of NO (14). Moreover, the anti-inflammatory properties of Suma are mediated by reduction in the release of neuropeptides such as calcitonin gene-related peptide and substance P, which are effective against the inflammatory factors (15).

Thus, the purpose of our study was to explore whether Suma affects the Cis-induced kidney damage in mice by studying oxidative stress indices and histological alterations.

Materials and Methods

Animals

Twenty-eight male mice (weighing 25-30 g, 6-7 weeks old) were used in this study. Animals were maintained under standard conditions (22±2 °C temperature; 12-12 hr light/dark cycle) with free access to standard laboratory food and purified drinking water. All procedures were conducted according to the ethical guideline of Rafsanjan University Research (Ethic code: IR.RUMS.REC.1396.85).

Chemicals

Suma was obtained from Sigma-Aldrich (Germany)

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and Cis (CISPLATIN MYLAN®) was obtained from MYLAN Company (France). Drugs were administrated intraperitoneally (IP), and Suma was freshly dissolved in normal saline (9% sodium chloride).

Experimental design

Mice were randomly separated into four groups (n = 7). Group I (control group) received no treatment. Group II (Cis group) received Cis (20 mg/kg) on the first day of the experiment. Group III and IV (Suma 0.1 and Suma 0.3) received Cis on the first day of the experiment, and Suma at the doses of 0.1 and 0.3 mg/kg/day was started on day 1 and continued for 3 consecutive days. The route of administration and dosages were selected from previous works (16, 17).

Sample collection

On day 4 of the experiment, blood samples were collected from the orbital sinus under diethyl-ether anesthesia. The blood samples were centrifuged at 3000 rpm for 10 min to separate serum. The serum samples were stored at -20 ℃ for measurement of BUN and Cr. Then, animals were sacrificed by rapid decapitation and both kidneys were immediately removed and washed with cold normal saline. For pathological studies, the left kidney was fixed in 10% neutral buffered formalin. For biochemical assessments, the right kidney was shock-frozen in liquid nitrogen and kept at –80 ℃.

Serum parameters

The serum levels of BUN and Cr were measured using the biochemical autoanalyzer (MINDRAY, China) with respective commercial kits (Bayer S.A. Diagnostic).

Biochemical assays

The kidneys were defrosted, homogenized with phosphate-buffered saline (1/10 w/v) and centrifuged at 6000 rpm for 20 min in 4 ℃. The supernatants were collected for the biochemical assays such as MDA level and SOD and GPx activities using commercial kits specific for mice (ZellBio, Germany).

Pathological evaluations

For pathological assessment, the kidney samples were fixed in formalin (10%), then kidney samples were dehydrated, embedded in paraffin and sectioned (5 μm). The sections were stained with hematoxylin & eosin (H&E) and observed under a light microscope (Nikon Labophot, Japan) by an expert pathologist for the presence of tubular cells vacuolation, tubular degeneration, tubular necrosis and cast (18). The

severity of these indices was scored into 4 categories: normal=0, mild=1, moderate=2 and severe=3 and the average values were reported (19).

Statistical analysis

Graphpad Prism software version 6 was used for statistical analysis (Graphpad Software, USA). The results are expressed as mean±SEM. Differences between groups were determined using ANOVA followed by Tukey's *post hoc* analysis. Non-parametric variable (pathological indices) were analyzed by Kruskal-Wallis test followed by Dunn's *post hoc* analysis. P value less than 0.05 was considered to be significant.

Results

Renal function

As shown in Figure 1, the levels of Cr and BUN significantly increased in the Cis group in comparison with the control group ($P<0.001$ in all groups). Administration of Suma at both doses (0.1 and 0.3 mg/kg) significantly decreased the BUN levels in Cis-administered mice ($P<0.001$ and $P<0.01$, respectively) (Figure 1A). Moreover, treatment with Suma (0.1 and 0.3 mg/kg) for 3 consecutive days significantly decreased the Cr in Cis-administered mice ($P<0.001$ in all groups) (Figure 1B).

Renal lipid peroxidation

Our results indicated that administration of Cis significantly increased the concentration of MDA in the Cis group compared to normal mice ($P<0.001$) (Figure 2). On the other hand, treatment with Suma (0.3 mg/kg) significantly reduced MDA level in comparison with the Cis-administered mice ($P<0.01$).
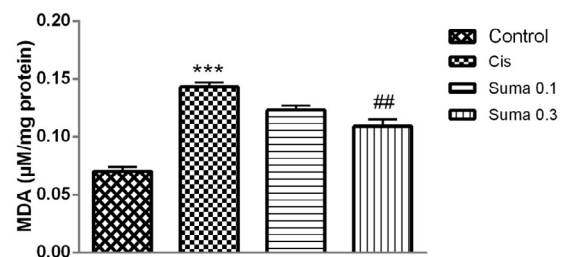
Figure 2. The effect of treatment with Suma on MDA concentration in Cis-induced nephrotoxicity. Values are means±SEM (n=7). Mice received no treatment, Cis (20 mg/kg) or Cis and Suma (0.1 and 0.3 mg/kg for 3 consecutive days), and kidneys were harvested after 96 hr. * Significant difference in comparison with the control group (***$P<0.001$); # Significant difference in comparison with the Cis group (##$P<0.01$). Cis: Cisplatin; Suma: Sumatriptan; MDA: Malondialdehyde
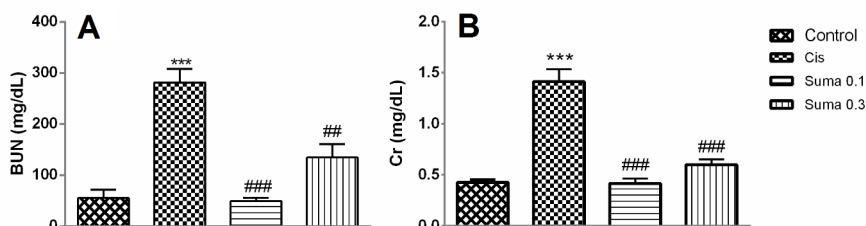
Figure 1. The effect of treatment with Suma on BUN (A) and Cr (B) levels in Cis-induced nephrotoxicity. Values are means±SEM (n=7). Mice received no treatment, Cis (20 mg/kg) or Cis and Suma (0.1 and 0.3 mg/kg for 3 consecutive days), and kidneys were harvested after 96 hr. * Significant difference in comparison with the control group (***$P<0.001$); # Significant difference in comparison with the Cis group (##$P<0.01$ and ###$P<0.001$). Cis: Cisplatin; Suma: Sumatriptan; BUN: Blood urine nitrogen; Cr: Creatinine

Table 1. Effect of sumatriptan on kidney histopathology in cisplatin-induced nephrotoxicity in mice

Groups	Histological criteria			
	Cast	Tubular necrosis	Tubular degeneration	Tubular cells vacuolation
Control	0±0	0±0	0±0	0±0
Cis	1.83±0.30**	2.16±0.3***	2.83±0.16***	2.16±0.16*
Suma 0.1	0.33±0.21#	1.16±0.16	1.33±0.21	1.16±0.30
Suma 0.3	0.16±0.16##	0.5±0.22#	0.66±0.21#	0.42±0.20#

Values are means±SEM (n=7)
* Significant difference in comparison with the control group (*$P<0.05$, **$P<0.01$ and ***$P<0.001$)
# Significant difference in comparison with the Cis group (#$P<0.05$ and ##$P<0.01$)
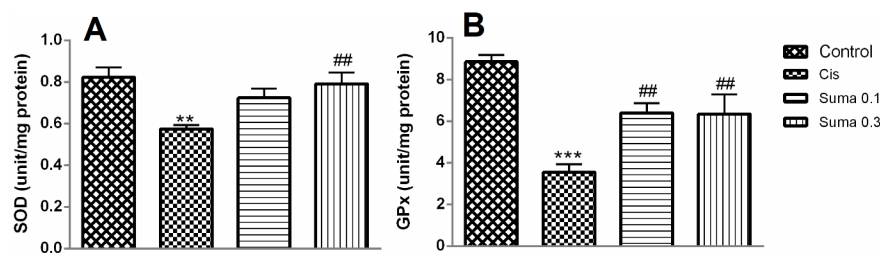Cis: Cisplatin; Suma: Sumatriptan

Figure 3. The effect of treatment with Suma on SOD (A) and GPx (B) in Cis-induced nephrotoxicity. Values are means±SEM (n=7). Mice received no treatment, Cis (20 mg/kg) or Cis and Suma (0.1 and 0.3 mg/kg for 3 consecutive days), and kidneys were harvested after 96 hr. * Significant difference in comparison with the control group (**$P<0.01$ and ***$P<0.001$); # Significant difference in comparison with the Cis group (##$P<0.01$). Cis: Cisplatin; Suma: Sumatriptan; SOD: Superoxide dismutase; GPx: Glutathione peroxidase

Renal antioxidant enzyme activities

The SOD and GPx activities were significantly reduced in the Cis group compared to the normal mice ($P<0.001$ in all groups) (Figure 3). Moreover, Suma administration (0.3 mg/kg) for 3 consecutive days increased the SOD activity in comparison with the Cis-administered mice ($P<0.01$) (Figure 3A). Furthermore, administration of Suma at both doses (0.1 and 0.3 mg/kg) significantly increased the activity of GPx in comparison with the Cis-administered mice ($P<0.01$ in all groups) (Figure 3B).

Renal pathology

The kidney samples of control group presented normal kidney morphology. In this group, the lumen of the collecting tubules (bent arrow) were obvious and no evidence of tubular injury such as cast, necrosis, degeneration and vacuolation was observed (Figure 4A; Table 1). The kidney sample of Cis group displayed massive tubular injury in the form of tubular degeneration (lightning bolt), tubular cells vacuolation (line arrow), tubular necrosis (white arrow) and
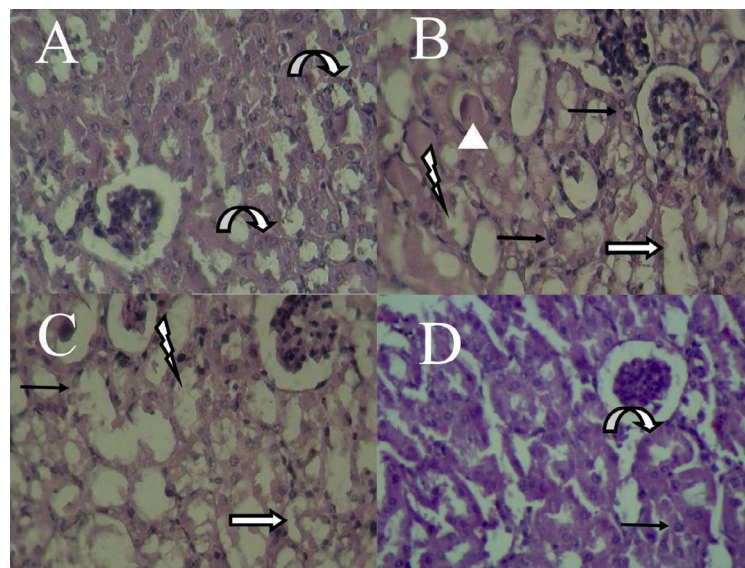

Figure 4. Histopathological observations showing the effects of Suma on Cis-induced nephrotoxicity changes in kidney. Mice received no treatment, Cis (20 mg/kg) or Cis and Suma (0.1 and 0.3 mg/kg for 3 consecutive days), and kidneys were harvested after 96 hr (kidney sections stained with Hematoxylin & Eosin, magnification X 400). (A) Control group; (B) Cis group; (C) Suma 0.1 group; (D) Suma 0.3 group. Cis: Cisplatin; Suma: Sumatriptan. Bent arrow: lumen of the normal collecting tubules; Lightning bolt: tubular degeneration; Line arrow: tubular cells vacuolation; White arrow; tubular necrosis; Triangle: cast

cast (triangle) (*P*<0.05 for tubular cells vacuolation, *P*<0.01 for cast and *P*<0.001 for tubular necrosis and tubular degeneration) (Figure 4B; Table 1). Moreover, administration of Suma at the dose of 0.1 mg/kg only reduced the cast (*P*<0.05), but tubular degeneration, cells vacuolation and necrosis were unaffected. In this group, the collecting tubules were more obvious than Cis group (Figure 4C; Table 1). Furthermore, Suma (0.3 mg/kg) effectively reduced the Cis-induced tubular injury and all tubular injury parameters were reduced in these groups (*P*<0.05 for tubular cells vacuolation, tubular necrosis and tubular degeneration and *P*<0.01 for cast). In Suma 0.3 group, the lumen of collecting tubules were obvious, but tubular cells vacuolation was observed. Also, there was no evidence of tubular degeneration, tubular cells vacuolation, tubular necrosis and cast (Figure 4D; Table 1).

Discussion

In the current study, the effect of Suma treatment on nephrotoxicity induced by Cis was investigated. Our results demonstrated that IP administration of Cis causes considerable renal injury as evidenced by increase in the levels of BUN and Cr. In line with previous studies, after injection of Cis with the mentioned dose, the MDA level was increased and the SOD and GPx activity were reduced in renal tissue (20, 21). Moreover, the results of renal pathological assessment correlated with changes in biochemical indices. It was also observed that coadministration of Suma (especially 0.3 mg/kg, IP) and Cis prevents nephrotoxicity in mice through decreasing the levels of MDA, Cr and BUN as well as increasing the activities of GPx and SOD. Moreover, IP administration of Suma significantly mitigated the Cis-induced pathological changes of the renal tissues.

We used BUN and Cr levels as common biochemical tests for evaluation of the kidney functions. A large body of evidence has implicated that Cis-induced elevation of Cr and BUN levels are associated with the increase in the ROS formation (superoxide and hydroxyl radicals) in the kidney tissue (5, 21). On the other hand, Cis increases the production of NO in the kidney (22). It has been found that antioxidant substances such as lycopene and ellagic acid attenuate the elevation of Cr and BUN levels in Cis-induced nephrotoxicity (20, 21, 23). Moreover, it was reported that Suma scavenges superoxide and hydroxyl radicals as well as NO (13). Furthermore, it is well-established that Suma blocks the NO pathway, which is a major mechanism underlying the anti-migraine properties of Suma (24). Accordingly, it seems that Suma may exert its nephroprotective effects via attenuation of the renal oxidative stress.

We observed that Suma significantly attenuates MDA in kidney of mice treated with Cis. Overproduction of free radicals plays a critical role in nephrotoxicity induced by Cis, which is associated with increase of oxidative stress parameters in renal tissue such as MDA (1, 25, 26). MDA is a confirmed biomarker for cellular damage (27). It is well-documented that Suma could inhibit pro-oxidative enzymes such as inducible nitric oxide synthase (iNOS) and lipid peroxidase (28). Furthermore, Suma is a strong antioxidant compound, which directly neutralizes free radicals like hydroxyl and superoxide radicals (29). Hence, Suma may reduce MDA directly by reduction of lipid peroxidation and/or indirectly by suppression of free radicals production.

SOD catalyzes the conversion of superoxide radical to H_2O_2. Then, H_2O_2 is detoxified in cells by GPx (30). Cis causes the oxidative stress, which leads to reduction of renal antioxidant capacity (20, 21). It has been shown that inhibition of the antioxidant defense mechanisms is involved in pathogenesis and progression of migraine; this implies that the therapeutic effects of Suma on migraine might be mediated through increased activity of brain antioxidant defense (31, 32). For the first time, we revealed that Suma administration (more potently 0.3 mg/kg) increases the renal enzymes of antioxidant system such as GPx and SOD.

Our histopathological findings are in parallel with the biochemical results. Cis causes renal morphological and functional lesions via overproduction of free radicals (19, 33, 34). Moreover, previous studies confirm that Cis mainly induces tubular damage (35-38). We also confirmed that Cis causes cast, tubular necrosis, tubular cells vacuolation and tubular degeneration. The nephroprotective effects of Suma were also confirmed by pathological evaluations, which indicated significant attenuation in pathological indices in Cis-administered mice.

It has been reported that Suma induces adverse effects within the central nervous system (CNS) such as memory impairment, anxiety and panic disorder (9). On the other hand, it has been found that Suma exerts protective effects on peripheral neuropathy induced by vincristine (39).

Conclusion

For the first time, we showed that Suma has nephroprotective effect in Cis-induced nephrotoxicity. According to the results of our study, it can be concluded that Suma may protect the cancer patients against the nephrotoxicity of Cis. However, more studies are needed to reveal the precise molecular mechanisms underlying Suma effects on Cis-induced nephrotoxicity.

Conflicts of Interest

All authors repot no conflict of interest.

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