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Original Article

Role of arginine and/or taurine in protection against gentamicin-induced nephrotoxicity in male and female rats

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Abstract

Background

As a highly effective antibiotic, gentamicin is used in the treatment of serious and life-threatening gram-negative infections. L-arginine (2-amino-5-guanidino-pentanoic acid) has a protective role on renal failure that induced by gentamicin administration and it may decrease the tubular reabsorption of another cationic substance, gentamicin due to its cationic structure. The aim of this study is to determine the influence of gender on nephroprotective effects of L-arginine (Arg) and/or taurine (Tau) on gentamicin (G) induced nephrotoxicity.

Methods

Adult Sprague-Dawley albino rats of both sexes (150-200 g, 48 male and 48 female), were bred from the animal unit of National Nutrition Institute, Cairo, Egypt. Male rats were divided randomly into 8 groups (n=6 per group) and the following treatments were given: Group 1 (negative control group): saline (2 ml/Kg/day, i.p); Group 2 (positive control group): was injected with G (100 mg/kg b.wt./day, i.p); Group 3 injected with G and treated with Arg (1.6 gm/kg b.wt /day, p.o); Group 4 injected with G and treated with Tau (0.75 gm/kg b.wt/day,i.p) and Group 5 injected with G and treated with combination of Arg and Tau at the same previously mentioned doses. The tested amino acids and their combination were also administrated to healthy rats (three groups) for ten consecutive days. Female rats were divided at random into eight groups and treated in the same fashion as above.

Results

Gentamicin administration resulted in nephrotoxicity as evidenced by significant elevation in serum creatinine (122% and 127%) and blood urea nitrogen (BUN) (18.3% and 117%), significant reduction in creatinine clearance (30% and 46.9%), proteinuria (250% and 372%), sharply elevated levels of urinary alkaline phosphatase (ALP) (267% and 415%) and potassium (244% and 376%) and decreased level of serum ALP (10.2% and 31.9%) in males and females, respectively. Gentamicin did not affect serum potassium in both males and females and on serum sodium in males; however, it increased serum sodium in females by 27%. Also, gentamicin injection enhanced lipid peroxidation as indicated by the elevated levels of renal malondialdehyde (MDA) (46.7% and 22.8%) and nitric oxide (NO) (48% and 72%) and the depressed level of reduced glutathione (GSH) in kidney (55% and 45%) and whole blood (5.7% and 8.8%) in male and female rats, respectively, as compared with normal rats. Also, the activity of erythrocyte Cu, Zn superoxide dismutase (SOD) was reduced (10.1%) in males but not in females as compared with normal rats. Supplementation with Arg and/or Tau attenuated G induced nephrotoxicity in male and female rats. These nephroprotective effects were more pronounced in females.

Conclusion

The results of the present study indicate that female Sprague-Dawley rats are more sensitive to the nephrotoxic effects of G. Treatment with Arg and/or Tau exerted a nephroprotective impact, which is gender specific.

Keywords: Arginine, sex differences, gentamicin, nephrotoxicity, taurine

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Introduction

Acute kidney injury owing to ischemic or toxic renal damage is a common disorder, with a mortality rate of ~50% [1]. Owing to high relative blood flow, the kidney is prone to drug-induced damage. Aminoglycoside-type antibiotic gentamicin is one of the leading cause of drug-induced nephrotoxicity [2]. As a highly effective antibiotic, gentamicin is used in the treatment of serious and life-threatening Gram-negative infections. However, its clinical usefulness is limited by its nephrotoxicity, which may occur in ~13–30% of treated patients [3]. Numerous factors may influence the capacity of aminoglycoside to evoke nephrotoxic effects, and sex is one of these factors [4]. Previous studies on animals and humans showed no conclusive findings regarding the effect of sex on aminoglycoside-induced nephrotoxicity. It was found that male Fischer 344 rats are more sensitive to the toxic effects of gentamicin than their female counterparts [5]. In contrast, it has been reported that there is no significant sex difference in the magnitude of gentamicin-induced nephrotoxicity in Sprague-Dawley rats, although the treated male rats exhibited higher renal cortex accumulation of gentamicin than female ones [6]. In humans, females were reported to be affected by gentamicin nephrotoxicity more than males [7].

l-Arginine (Arg) (2-amino-5-guanidino-pentanoic acid) is a conditionally essential amino acid. It is an important amino acid that participates in multiple biochemical processes in mammals. In addition to its implication in the urea cycle and protein synthesis, it serves as a precursor for the synthesis of amino acids, nitric oxide (NO), polyamines, creatine, agmatine, and other guanidino compounds [8]. Arg has some protective effects on GM-induced nephrotoxicity in female rats [9]. Arg supplementation has been used as a strategy to ameliorate the progression of kidney disease, presumably, because it increases NO production [10].

Taurine (Tau) is a β-amino acid naturally found in the kidneys [11]. It has been shown that Tau has a protective effect in several tissues [11,12] and serves as an antioxidant agent [12]. There are a few reports about the beneficial effect of Tau in kidney tissue. Erdem *et al.*[13] reported that Tau treatment attenuates the accumulation of gentamicin within kidney tissue and counteracts the deleterious effect of gentamicin on renal tubular function.

This study aimed to investigate the influence of sex on the renal toxicity of gentamicin in Sprague-Dawley rats and furthermore to see if sex would affect the nephroprotective effects of Arg and/or Tau.

Materials and methods

Chemicals

El-Nile Company (Cairo, Egypt), kindly supplied gentamicin sulfate powder. Arg and Tau were purchased from the International Company for Scientific and Medical Supplies (Cairo, Egypt). Urea, creatinine, total protein, alkaline phosphatase (ALP), sodium, and potassium kits were purchased from Stanbio Laboratory 1261 N Main St, Boerne, TX 78006, United States. All other chemicals were of analytical grade.

Animals and treatments

Adult Sprague-Dawley albino rats of both sexes (150–200 g, 48 male and 48 female), were bred from the animal unit of National Nutrition Institute, Cairo, Egypt. The animals were housed individually in metallic cages under healthy condition. Water and basal diet were provided *ad libitum* for 1 week as an adaptation period and throughout the experimental period (10 days).

Male rats were divided randomly into eight groups ($n = 6$/group), and the following treatments were given: group 1 (negative control group) was given saline (2 ml/kg/day, intraperitoneally); group 2 (positive control group) was injected with Gentamicin G (100 mg/kg/body weight/day, intraperitoneally); group 3 was injected with G and treated with Arg (1.6 g/kg/body weight/day, orally); group 4 was injected with G and treated with Tau (0.75 g/kg/body weight/day, intraperitoneally), and group 5 was injected with G and treated with combination of Arg and Tau at the same previously mentioned doses. The tested amino acids and their combination were also administrated to healthy rats (three groups) for 10 consecutive days. Female rats were also divided at random into eight groups and treated in the same fashion as stated before.

The dose of G and the duration of treatment are based on the well-established model of G-induced renal damage described by Dhanarajan *et al.* [14]. The dose of Arg is according to De Nicola *et al.* [15], and that of Tau is according to Erdem *et al.* [13]. All injections were carried out between 9.00 and 11.00 a.m. to minimize the circadian variation in G nephrotoxicity [16].

After the last injection, animals from each group were kept individually in wire-bottom stainless steel metabolic cages for the collection of 24-h urine samples. During the period of urine collection, animals were overnight fasted and allowed free access to water only. The volumes of the collected urine samples were measured, recorded, and stored at −20°C until biochemical analysis.

At the end of the treatment period (24 h after the last injection), the animals were killed under diethyl ether anesthesia. The kidneys were removed, washed in cold saline, plotted in filter paper, weighed, and used for the biochemical assays. The serum was used for the biochemical assays. The heparinized blood samples were used for the determination of reduced glutathione (GSH). The erythrocytes were washed twice with cold saline and kept at −20°C for Copper Cu, Zinc Zn superoxide dismutase (SOD) estimation.

Biochemical assays

Blood urea nitrogen (BUN) and serum creatinine were determined by the methods of Bonsens and Taussky[17] and Patton and Crouch [18], respectively; total protein was assayed

according to Henry *et al.* [19]; ALP was estimated in serum and urine according to the methods of Tietz *et al.* [20]; and sodium and potassium were estimated by standard spectrophotometric methods according to Trinder[21] and Tietz [22], respectively. Malondialdehyde (MDA) (as an index of in-vivo lipid peroxidation) was measured in left kidney homogenate by the thiobarbituric reaction [23]. Nitric acid was determined according to Miranda *et al.* [24], with modification, using zinc sulfate[25] instead of ethanol for protein precipitation. GSH was determined according to the method of Beutler *et al.* [26]. The determination of Cu, Zn SOD activity was according to Winterbourne *et al.* [27].

Statistical analysis

The collected data were statistically analyzed using SPSS, version 11.0 (Chicago, Illinois: SPSS Inc. 2006). Results were expressed as mean ± SEM. One-way analysis of variance was used. The difference among group means was tested using the least significant differences at *P* value less than 0.05 [28].

Results

Normal male and female rats treated with Arg and/or Tau showed no statistically significant ($P > 0.05$) differences in the measured biochemical parameters as compared with the corresponding normal controls.

Data presented in Table 1 show that G administration resulted in nephrotoxicity as indicated by significantly ($P < 0.05$) elevated levels of serum creatinine (122 and 127%) and BUN (18.3 and 117%) and lowered levels of creatinine clearance (30 and 46.9%) in male and female rats, respectively, as compared with the corresponding normal controls.

Treatment with Arg or Tau had no significant effect ($P > 0.05$) on the concentration of serum creatinine in G-treated males, whereas concomitant Arg and Tau treatment significantly ($P < 0.05$) reduced it by 37%. However, G-treated female rats received Arg, Tau, or both of them displayed significant ($P < 0.05$) reduction in serum creatinine by 41, 6.6, and 17.3%, respectively. The lowered creatinine clearance was significantly ($P < 0.05$) increased in G-treated male rats that received Tau or both of Arg and Tau by 42 and 42%, respectively, and in G-treated female rats received Arg, Tau, or both of them by 85, 82, and 77%, respectively. BUN levels were significantly ($P < 0.05$) lowered in male rats (7.3, 27, and 49%) and female rats (38, 32, and 72%) treated with G and Arg or Tau or both of them, respectively, as compared with G-treated rats.

Male and female rats treated with G had serum ALP level, which was 10.2 and 31.9%, lower than the corresponding normal controls. Treatment with Arg or Arg and Tau significantly ($P < 0.05$) increased the reduced level of serum ALP by 7.9 and 11.3% in male and by 45.3 and 48% in female rats as compared with G-treated rats. Urinary ALP was sharply elevated in G-treated male and female rats by 267 and 415%, respectively, as compared with corresponding normal controls. Male rats treated with

Table 1: Effects of arginine and/or taurine on serum creatinine, creatinine clearance, and blood urea nitrogen in gentamicin-induced nephrotoxicity in male and female rats

Parameters	Treatments					
	Serum creatinine (mg/dl)		Creatinine clearance (ml/min/100 g/body weight)		Blood urea nitrogen (mg/dl)	
	Male	Female	Male	Female	Male	Female
Saline	0.7±0.02	0.66±0.02	0.4±0.02	0.66±0.02	20±0.93	19.74±0.96
G	1.56±0.04[a]	1.5±0.05[a]	0.28±0.02[a]	0.35±0.03[a]	23.67±1.0[a]	43±0.08[a]
G+Arg	1.17±0.03[a]	0.88±0.04[b]	0.33±0.03	0.65±0.02[b]	21.92±1.2[b]	26.61±1.6[a,b]
G+Tau	1.54±0.05[a]	1.4±0.07[a,b]	0.4±0.02[b]	0.64±0.03[b]	17.1±1.1[b]	28.9±1.2[a], [b]
G+Arg+Tau	0.97±0.05[b]	1.24±0.03[a,b]	0.4±0.02[b]	0.62±0.03[b]	12.03±0.9[a,b]	11.97±0.83[a,b]

Values are mean±SEM of six rats. Arg, arginine; G, gentamicin; Tau, taurine. [a]Significant differences from the corresponding negative control at $P<0.05$. [b]Significant differences from the corresponding positive control at $P<0.05$.

Table 2: Effects of arginine and/or taurine on serum and urinary alkaline phosphatase and total protein in gentamicin-induced nephrotoxicity in male and female rats

Parameters	Treatments							
	Serum alkaline phosphatase (U/l)		Urinary alkaline phosphatase (U/mmol creatinine)		Serum total protein (g/dl)		Urinary protein (g/24 h)	
	Male	Female	Male	Female	Male	Female	Male	Female
Saline	98±61.2	94±1.4	17.12±0.88	20±0.94	8.5±0.25	8.3±0.26	0.06±0.01	0.055±0.01
G	88±1.56[a]	64±1.34[a]	62.84±1.13[a]	103±0.89[a]	7±0.38	6.9±0.4	0.21±0.02[a]	0.26±0.01[a]
G+Arg	95±1[b]	93±1.2[b]	19±1.12[b]	25±0.73[a,b]	7.8±0.3	8.4±0.27	0.11±0.02[b]	0.05±0.015[b]
G+Tau	90±1.44[a]	64±0.99[a]	61.51±0.96[a]	99±0.9[a,b]	8.9±0.38	8.6±0.21	0.05±0.01[b]	0.04±0.02[b]
G+Arg+Tau	98±0.97[b]	95±0.73[b]	16.86±0.73[b]	17±0.78[a,b]	8.4±0.2	7.9±0.2	0.09±0.01[b]	0.19±0.014[a,b]

Values are mean±SEM of six rats. Arg, arginine; G, gentamicin; Tau, taurine. [a]Significant differences from the corresponding negative control at $P<0.05$. [b]Significant differences from the corresponding positive control at $P<0.05$.

Table 3: Effects of arginine and/or taurine on serum and urinary sodium and potassium in gentamicin-induced nephrotoxicity in male and female rats

Parameters	Treatments							
	Serum sodium (mmol/l)		Urinary sodium (mmol/24 h)		Serum potassium (mmol/l)		Urinary potassium (mmol/24 h)	
	Male	Female	Male	Female	Male	Female	Male	Female
Saline	144±1.2	100±0.64	1.21±0.02	0.97±0.04	6.1±0.12	5.9±0.11	0.25±0.01	0.25±0.01
G	147±0.8	127±0.96[a]	0.82±0.02[a]	0.76±0.06	5.5±0.09	4.2±0.09	0.86±0.01[a]	1.19±0.01[a]
G+Arg	146±0.8	119±0.91[a,b]	0.81±0.04[a]	0.84±0.04	5.5±0.08	5.8±0.07	0.47±0.02[b]	0.52±0.01[b]
G+Tau	143±1.1	122.8±1.2[a]	0.94±0.04	0.73±0.03	5.6±0.02	4.5±0.05	0.76±0.04[a]	1.0±0.02[a]
G+Arg+Tau	148±1.1	128.5±0.9[a]	0.78±0.04[a]	0.64±0.06[a]	5.9±0.08	5.3±0.07	0.28±0.03[b]	0.79±0.02[a,b]

Values are mean±SEM of six rats. Arg, arginine; G, gentamicin; Tau, taurine. [a]Significant differences from the corresponding negative control at $P<0.05$. [b]Significant differences from the corresponding positive control at $P<0.05$.

G and Arg or both Arg and Tau showed significant ($P < 0.05$) reduction in urinary ALP by 69 and 73%, respectively. However, in female rats, urinary ALP was significantly ($P < 0.05$) reduced by administration of Arg (75%), Tau (4%), or both of them (83%) as compared with G-treated rats (Table 2).

Treatment with G or G and amino acids had no significant ($P > 0.05$) effect on serum total protein. However, urinary protein was significantly ($P < 0.05$) elevated in male and female rats by 250 and 372%, respectively, as compared with corresponding normal controls. Treatment with G and Arg or Tau or both of them resulted in significant ($P < 0.05$) reduction in urinary protein by 47, 76, and 57%, respectively, in male rats and by 80.7, 84.6, and 26.9% in female rats, respectively, as compared with G-treated rats.

Gentamicin injection increased serum sodium in both male and female rats, but this increase was significant ($P < 0.05$) only in female rats (27%), and there was significantly ($P < 0.05$) reduced urinary sodium excretion in males (32%) and females (21%) as compared with the corresponding normal controls. Treatment with Arg significantly ($P < 0.05$) reduced the elevated serum sodium in female rats by 6.2%. The tested amino acids had no significant ($P > 0.05$) effects on the concentration of sodium in serum in male rats or on sodium excretion in urine in both male and female rats (Table 3).

Treatment with G or G and the tested amino acids had no significant effect on serum potassium in both male and female rats as compared with the corresponding normal controls. However, urinary potassium was significantly ($P < 0.05$) increased by 244 and 376% in male and female rats treated with G, respectively, as compared with the corresponding negative controls. The elevation in urinary potassium excretion was reduced in male and female rats treated with Arg (45 and 56%) and combination of Arg and Tau (67.4 and 33.6%), respectively, as compared with the corresponding positive controls.

Male and female rats treated with G showed significant ($P < 0.05$) elevation in renal MDA by 46.7 and 22.8% and renal NO by 48 and 72% and significant ($P < 0.05$) reduction in renal GSH by 55 and 45% and whole blood GSH by 5.7 and 8.8%, respectively, as compared with corresponding negative controls. Moreover, erythrocyte Cu, Zn SOD activity was reduced by 10.1% in males, but it was not affected in females as compared with corresponding negative controls.

Administration of Arg or Tau or both Arg and Tau significantly ($P < 0.05$) reduced the elevated levels of renal MDA in both G-treated male (30, 57, and 12%) and female (47, 59, and 28%) rats. Moreover, the tested amino acids significantly ($P < 0.05$) reduced renal NO in female rats by 20, 7, and 29%, respectively. Renal NO was significantly ($P < 0.05$) reduced in male rats treated with Arg (14%) and a combination of both Arg and Tau (32%).

f × 1
f × 2
f × 3
f × 4
f × 5

Discussion

In this study, sex has a different effect on the vulnerability of Sprague-Dawley rats to G nephrotoxicity. Female rats are more sensitive to nephrotoxic effects of G than males. These results are in a good agreement with Carraro-Eduardo *et al.*[29] who reported that rats medicated with 40 mg/kg/24 h gentamicin for 10 days, showed functional kidney impairment, and these lesions were considerably more severe in female rats. Moreover, Chahoud *et al.*[30] reported that 1 year after treatment of pregnant rats with G, nephrotoxicity and hypertension occurred in the female offspring only. Moreover, these results are more or less similar to that reported by Sweileh[31] who found that human females are more sensitive to G-induced renal dysfunction than males. However, the present data are different from those reported by others [32], who found no sex differences in gentamicin nephrotoxicity in this strain of rats. The reason for this discrepancy is not certain but may be related to the differences within this strain of rats or other unknown reasons.

Mechanisms underlying sex differences in aminoglycoside-induced nephrotoxicity are difficult to explain. However, such a difference could be ascribed to hormonal and/or pharmacokinetic differences between both sexes [3,31].

Several correlations between renal brush border membrane binding affinity of aminoglycoside and aminoglycoside nephrotoxicity have been cited including the higher binding affinity in male versus female rats [33]. However, it has repeatedly been shown that there is no correlation between the nephrotoxicity of G and its absolute accumulation in renal tissues [34]. Pre-renal hepatic metabolism in which there may be strain and/or sex differences has also been suggested as a necessary component of aminoglycosides-induced nephrotoxicity [35]. However, this seems unlikely as it has been shown that the aminoglycosides are not metabolized *in vivo* [36].

The role of NO in renal function is controversial. In this regard, our findings are compatible with the report of Christo *et al*. [37], which found that after 10 days of GM administration, serum Cr and urea level increased. In the same way, nitrite serum level increased and its urinary level reduced. However, in contrast with our findings, two studies showed that the protective properties of Arg had been observed in male albino rats in GM-induced renal failure [38].

Animal models suggest differences in dependence of the renal vasculature on NO, depending on sex. Verhagen *et al.*[39] demonstrated that mild nitric oxide synthase (NOS) inhibition resulted in significantly higher increases in proteinuria in male rats compared with female rats. The kidneys of male Han: SPRD rats, a model of polycystic renal disease, are susceptible to the effects of nitro-Arg methyl ester, although the kidneys of their female counterparts are not [40]. Erdely *et al.*[41] reported that elderly male Sprague-Dawley rats had reduced renal NOS activity and NOS protein abundance compared with both age-matched female rats and young male rats. In a rat model of renal wrap hypertension, Ji *et al.*[42] demonstrated more severe renal injury in male compared with female rats and attributed this sexual dimorphism to differences in renal endothelial and neuronal NO production. However, these correlations contradict our finding as females were more susceptible to nephrotoxicity than males.

Verhagen *et al.*[39] showed that male as well as female sex hormones play a role in sex-related differences in sensitivity to develop proteinuria. In addition to the effects of sex hormones on NO availability, it has been shown that estrogens as well as testosterone influence many other processes involved in progression of renal disease, including mesangial cell proliferation and matrix accumulation, as well as the synthesis and release of cytokines, vasoactive agents, and growth factors [43].

Moreover, differences in kidney structure and function can contribute to differences in sensitivity for renal injury between males and females. Glomerular volume is more significant in males than in females, and this difference is eliminated by castration [44]. Higher afferent and efferent arteriolar resistances have been reported in female rats compared with males in the absence of differences in arterial and glomerular pressure [45]. These inherent differences may also have contributed to the disparity between the sexes in G-induced nephrotoxicity [39].

In this study, administration of Arg to gentamicin-treated rats ameliorated renal injury as indicated by almost normalization of creatinine clearance and decreased serum creatinine and BUN, indicating an increase in glomerular filtration rate. Similar findings have been reported by others [46,47]. We propose the involvement of Arg metabolites in this protective effect, as it is known that polyamines are mediators of cell growth and that l-proline is involved in collagen synthesis, and both of these metabolites are known to play roles in tissue repair process [48].

The results of this study demonstrated that the nephroprotective effects of Arg were more apparent in female rats than males. Ruzafa *et al.*[49] found that there is a marked sex dimorphism in the levels of Arg in plasma, kidney, and skeletal muscle, as female mice had higher levels than males. Moreover, the restriction of dietary Arg produced a marked decrease of Arg in plasma and tissues that almost abolished the sexual dimorphism found in the levels of this amino acid. This dietary restriction also affected the activities of enzymes related to the metabolism of Arg and ornithine that is regulated by sex hormones, suggesting the existence of some interaction between dietary Arg and hormone action [49]. Moreover, dietary Arg supplementation stimulates renal ornithine decarboxylase and kidney hypertrophy in male but not in female mice [50].

The data of the present study demonstrated that Arg counteracted the deleterious effects of gentamicin on oxidative stress markers such as decreased renal concentrations of MDA and NO levels and increased activity of SOD and levels of reduced GSH in kidney and whole blood. These results can be supported by the finding of Chander and Chopra[46] and Kurus *et al.* [47]. The observed increase in renal GSH in G + Arg-treated rats may be attributed to the induction of GSH synthesis. Such suggestion may be supported by the finding of Petrovic *et al.*[51] who found that Arg supplementation induces GSH synthesis in interscapular brown adipose tissue through the activation of glutamate-cysteine ligase expression. Recent studies suggest that supplemental Arg may help prevent harmful oxidation and reverse endothelial dysfunction [52]. Some of Arg's antioxidant and anti-inflammatory effects are independent of NO production [53].

It is clear from the present study that Tau exerted a renoprotective effect against gentamicin-induced nephrotoxicity as evident by marked amelioration effect on BUN, serum creatinine, and creatinine clearance, as well as serum and total urinary protein, sodium, potassium, and ALP. These beneficial effects of Tau on gentamicin-treated rats were more evident in females than males. These results are similar to those reported by Roysommuti *et al.*[54] who demonstrated that perinatal Tau supplementation could increase the mean arterial pressure in adult male rats but not female rats. Furthermore, perinatal Tau depletion can increase arterial pressure in adult female but not male rats. In addition, Koeners *et al.*[55] showed perinatal

exposure to the micronutrients Arg, Tau, vitamin C, and vitamin E in fawn-hooded hypertensive rats ameliorated the development of hypertension and proteinuria. Antihypertensive effects were more pronounced in male offspring, whereas renal protective effects were more pronounced in female offspring.

The observed effects of Tau could be attributed to its ability to resist cell damage in a nonspecific way by membrane stabilization and by osmoregulation [56]. Tau is a very important organic osmolyte in mammalian cells, including those of the kidney. It is a significant contributor to regulatory volume processes, such as the regulatory volume decrease and increases, which modulate cell volume and cell membrane stress following exposure of the cell to the hypoosmotic and hyperosmotic milieu, respectively [57].

In this study, Tau supplementation was also able to improve the elevated levels of renal lipid peroxidation and had an improvement effect on NO and reduced GSH levels in both kidney and whole blood. Moreover, Tau treatment induced a well-marked effect on the activity of Cu, Zn SOD. These results are matched with those of Yalçinkaya *et al.*[58] who reported that Tau was able to improve hyperhomocysteinemia-induced ROS production.

The free sulfhydryl group in Tau seems to play a significant role as a ROS scavenger. Tau is neither metabolized nor incorporated into cellular proteins in mammals suggesting ready availability of sulfhydryl moiety in the cytosol [12,59]. Antioxidant potential of Tau has also attributed to its ability to restore metal-induced depletion of membrane Na^+, K^+-ATPase activity [60]. The antioxidant effect of Tau can also be explained by its direct action to quench and detoxify some reactive intermediate such hypochlorous acid generated by myeloperoxidase [60], NO [61], and H_2O_2[62] and indirectly via protecting cells through intercalating into the membrane and stabilizing it. The membrane protecting the activity of Tau is suggested to be related to its action on permeability to ions and water [63]. Tau supplementation also provided significant recovery in depleted SOD activity. Taurine is synthesized from cysteine, the precursor of GSH. Hence, Tau supplementation may spare cysteine, thus increasing tissue levels of GSH [64].

Conclusion

The results of this study indicate that Sprague-Dawley female rats were affected by gentamicin nephrotoxicity more than males. Moreover, the administration of Arg and/or Tau has beneficial effects in rats with gentamicin-induced renal failure and that these effects are reversed by the NO synthase inhibition, and this was pronounced in females than males. The ameliorative action of Arg and/or Tau was more pronounced in female than in male rats.

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Conflicts of interest

There are no conflicts of interest.

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