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Sulfasalazine-induced renal and hepatic injury in rats and the protective role of taurine

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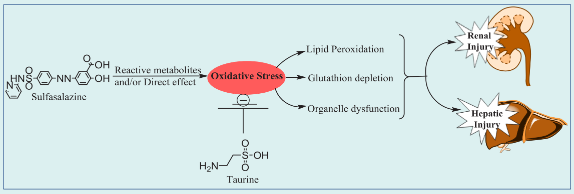
Abstract



Introduction: Sulfasalazine is a drug commonly administrated against inflammatory-based disorders. On the other hand, kidney and liver injury are serious adverse events accompanied by sulfasalazine administration. No specific therapeutic option is available against this complication. The current investigation was designed to evaluate the potential protective effects of taurine against sulfasalazine-induced kidney and liver injury in rats.

Methods: Male Sprague-Dawley rats were administered with sulfasalazine (600 mg/kg, oral) for 14 consecutive days. Animals received different doses of taurine (250, 500 and 1000 mg/kg, i.p.) every day. Markers of organ injury were evaluated on day 15th, 24 h after the last dose of sulfasalazine.

Results: Sulfasalazine caused renal and hepatic injury as judged by an increase in serum level of creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP). The levels of reactive oxygen species (ROS) and lipid peroxidation were raised in kidney and liver of sulfasalazine-treated animals. Moreover, tissue glutathione reservoirs were depleted after sulfasalazine administration. Histopathological changes of kidney and liver also endorsed organ injury. Taurine administration (250, 500 and 1000 mg/kg/day, i.p) alleviated sulfasalazine-induced renal and hepatic damage.

Conclusion: Taurine administration could serve as a potential protective agent with therapeutic capabilities against sulfasalazine adverse effects.

Introduction

Sulfasalazine is widely administered against rheumatoid arthritis and other inflammatory-mediated disorders such as Crohn's disease in the human.[1] On the other hand, several cases of liver injury associated with sulfasalazine therapy have been reported.[2-4] Hepatic injury induced by sulfasalazine might lead to hepatic failure and requirement for liver transplantation, and even patient death.[5-7] Some investigations also indicated impairment in renal function after sulfasalazine therapy.[8,9] Sulfasalazine-induced renal injury might be potentially irreversible.[10,11] No specific therapeutic agent has been developed against sulfasalazine-induced organ injury.

The precise mechanism of sulfasalazine-induced kidney and liver injury is unknown. Some investigations indicated the role of reactive oxygen species and oxidative stress in the organ injury induced by this drug.[12,13] Furthermore, oxidative stress also has been reported to be involved in infertility as another side effect of sulfasalazine.[14] As oxidative stress seems to be one of the mechanisms of sulfasalazine-induced organ injury,[12,13] it could be expected that administration of some antioxidants might be a therapeutic approach. Hence, chemicals that possess multifactorial protective activity including antioxidant properties may offer pharmacological value against sulfasalazine-induced organ injury.

Taurine (2-aminoethane sulfonic acid) is one of the most abundant amino acids in the human body. Although taurine is not a constituent of any structural proteins, many important physiological roles are attributed to this molecule. Taurine has been proposed to be a cell membrane stabilizer, intracellular ion regulator, and antioxidant.[15-17] Taurine has been considered for the treatment of a wide range of disease including epilepsy,[18] diabetic complications,[19] and cardiovascular disorders,[20] even though the underlying mechanisms involved were often unclear.

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Many investigations also indicated the hepatoprotective properties of taurine against xenobiotics-induced liver injury, including several drugs.[17,21,22] Furthermore, there are several reports about the beneficial effects of taurine in renal disorders.[23] It has also been found that taurine administration protected kidney against xenobiotics-induced renal injury.[24-27]
The current study was designed to investigate the potential protective role of taurine supplementation against sulfasalazine-induced renal and hepatic injury.

Material and methods

Chemicals

Taurine (2-amino-ethane sulfonic acid) was obtained from Acros (New Jersey, USA). Trichloroacetic acid (TCA),Thiobarbituric acid (TBA), Ethylenediaminetetraacetic acid (EDTA), phosphoric acid, 2-Amino-2-hydroxymethyl-propane-1, 3-diol (Tris) were obtained from Merck (Darmstadt, Germany). Kits for evaluating biomarkers of renal and liver injury were obtained from Pars Azmun (Tehran, Iran). All salts used for preparing buffer solutions were of analytical grade and obtained from Merck (Darmstadt, Germany).

Animals

Male Sprague-Dawley rats weighing 200-300 g were obtained from the Laboratory Animal Breeding Center, Shiraz University of Medical Sciences, Shiraz, Iran. Animals were housed in plastic cages over hardwood bedding. There was an environmental temperature of 21-23°C with a 40% of relative humidity. Animals had free access to a normal standard chow diet and water.

Experimental setup

Animals were randomly divided into six groups containing six rats in each. Rats were treated as follows: 1) Control (Vehicle-treated group), 2) Sulfasalazine (600 mg/kg, oral), 3) Sulfasalazine (600 mg/kg, oral) + Taurine (250 mg/kg, i.p), 4) Sulfasalazine (600 mg/kg, oral) + Taurine (500 mg/kg, i.p), 5) Sulfasalazine (600 mg/kg, oral) + Taurine (1000 mg/kg, i.p), and 6) Taurine (1 g/kg, the highest dose of taurine, i.p).
We administered sulfasalazine at a dose of 600 mg/kg/day for 14 consecutive days which is a dosage scheme reported to cause kidney and liver injury in rats.[12] At the end of experiments, animals were anesthetized (sodium thiopental, 80 mg/kg, i.p.) and their blood, kidney, and liver were collected.

Serum biochemistry and organ histopathology

Mindray BS-200® auto analyzer and standard kits (Pars Azmun®) were used to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and cratinine in animals serum[28]. For histopathological assessments, samples of kidney and liver were fixed in buffered formalin solution (0.4% sodium phosphate monobasic, NaH_2PO_4, 0.64% sodium phosphate dibasic, Na_2HPO_4, and 10% formaldehyde in distilled water). Paraffin-embedded sections of tissue were prepared and stained with hematoxylin and eosin (H&E) before light microscope viewing.[29]

Reactive oxygen species (ROS) formation

Reactive oxygen species in kidney and liver tissue was estimated by the method described by Gupta et al with some modifications.[30] Kidney and liver tissues was homogenized inice-cold Tris-HCl buffer (40 mM, pH=7.4) (1:10 w/v). Samples of the resulted tissue homogenate (100 µL) were mixed with Tris-HCl buffer (1 mL) and 5 µL of 2′, 7′-dichlorofluorescein diacetate (10 µM). The mixture was incubated for 30 minutes in 37°C (Gyromax™ incubator shaker). Finally, the fluorescence intensity of the samples was assessed using a FLUOstar Omega® multifunctional microplate reader with $\lambda_{excitation}$=485 nm and $\lambda_{emission}$=525 nm.[30,31]

Measurement of lipid peroxidation

The amount of lipid peroxidation in rat kidney and liver was assessed by measuring thiobarbituric acid reactive substances (TBARS). The reaction mixture consists of thiobarbituric acid (0.375%, w/v), phosphoric acid (1% w/v, pH=2), and 500 µL of tissue homogenate (10% w/v in KCl, 1.15%). The mixture was heated in boiling water (100°C) for 45 min. After the incubation period, the mixture was cooled, then 2 ml of n-butanol was added and vigorously mixed. Finally, samples were centrifuged (10000 g for 5 min) and the absorbance of developed colorin n-butanol phase was read at 532 nm using an Ultrospec 2000®UV spectrophotometer.[32]

Kidney and liver glutathione content

Tissue samples (200 mg) were homogenized in 8 mL of ice-cooled EDTA (20 mM). Five milliliters of the prepared homogenate were mixed with 4 mL of distilled water and 1 mL of trichloroacetic acid (50% w/v). The mixture was centrifuged (10000 g, 4°C, 25 min). Then, 2 mL of the supernatant was mixed with 4mL of Tris-HCl buffer (pH=8.9), and 100 µL of DTNB (0.01 M in methanol). The absorbance of developed color was measured in 412 nm using an Ultrospec 2000®UV spectrophotometer.[28]

Statistical analysis

Data are given as the Mean±SEM. Comparison of data sets were performed by the one-way analysis of variance (ANOVA) with Tukey's multiple comparison test as a *post hoc*. Differences were considered statistically significant when $p<0.05$.

Results

Sulfasalazine administration (600 mg/kg/day for 14 days) caused a marked impairment of liver function as judged by the elevated level of serum ALT, LDH, AST, and ALP (Table 1). Moreover, serum cratinine was also significantly raised in sulfasalazine-treated animals (Table 1).
It was found that sulfasalazine administration caused a

Table 1. Serum biomarkers of liver and kidney injury in sulfasalazine-treated rats and the role of taurine administration

Treatment	Markers assessed in rat serum				
	LDH (U/l)	ALT (U/l)	AST (U/l)	ALP (U/l)	Creatinine (mg/dl)
Control (Vehicle-treated)	366±65	38±7	81±10	344±61	0.25±0.03
+ Sulfasalazine 600 mg/kg/day	2457±459*	189±23*	338±31*	966±64*	0.65±0.04*
+ Taurine 250 mg/kg	334±75 #	42±3 #	92±9 #	174±12 #	0.47±0.08 #
+ Taurine 500 mg/kg	174±12 #	39±3 #	82±7 #	229±53 #	0.38±0.03 #
+ Taurine 1000 mg/kg	190±53 #	30±3 #	70±5 #	207±49 #	0.33±0.08 #

Data are given as Mean±SEM for six animals in each group.
*Significantly higher as compared to control (Vehicle-treated) (p<0.05).
#Significantly lower as compared to sulfasalazine-treated group (p<0.05).

significant increase in tissue level of reactive oxygen species (ROS) in both liver and kidney of tested animals (Fig. 1). Liver and kidney ROS formation was associated with consequent lipid peroxidation (Fig. 2) and glutathione reservoirs depletion (Fig. 3).

Histopathological evaluation of animals' liver revealed a slight increase in hepatic inflammatory cells aggregation in sulfasalazine-treated rats (Fig. 4). Although taurine administration effectively decreased the serum markers of liver injury, there were no significant changes in the inflammatory cells aggregation in the pre-portal area of the liver of sulfasalazine-treated animals when taurine was administered (Fig. 4).

Examination of renal tissue specimens revealed histopathological changes including interstitial inflammation, tubular atrophy and necrosis (Fig. 5) when animals were treated with sulfasalazine (600 mg/kg/day). Tubular atrophy was detected in taurine-treated (250, 500 and 1000 mg/kg) groups which received sulfasalazine, but there was no sign of tubular necrosis in these groups (Fig. 5).

Discussion

Sulfasalazine-induced renal and hepatic injuries are two serious adverse events accompanied by its clinical administration.[7-9,33] Although the mechanism(s) of organ injury induced by sulfasalazine is still unclear, defect in cellular defense mechanisms and reactive oxygen species formation are likely to be involved in the situation.[12,13]

Our findings of ROS formation and its consequent events including lipid peroxidation and tissue glutathione depletion confirms the occurrence of oxidative stress in liver and kidney after sulfasalazine administration.[12,13] These findings could support the notion that oxidative stress, at least in part, is involved in sulfasalazine-induced kidney and liver injury. The impairment in cellular defense mechanisms induced by sulfasalazine,[12,13] might lead to the generation of excess ROS and finally organ dysfunction. Multiple intracellular targets are subject to be affected by oxidative stress.[34] Sulfasalazine-induced production of ROS might finally interact with cellular macromolecules, cause

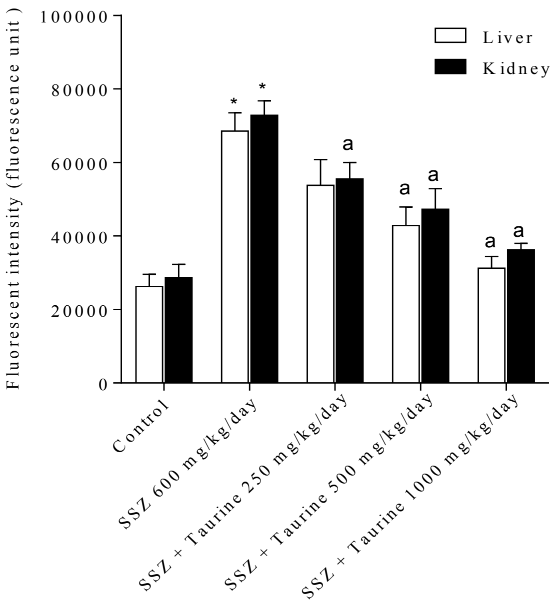

Fig. 1. Reactive oxygen species formation in liver and kidney tissue after sulfasalazine administration. SSZ: Sulfasalazine.
Data are presented as Mean±SEM for each group (n=6).
*Indicates significantly different as compared with control group (p<0.05). [a] Indicates significantly different as compared with sulfasalzine-treated group (p<0.05).

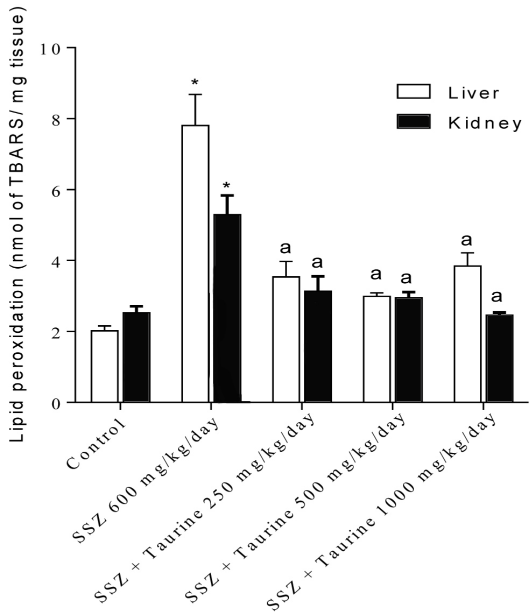

Fig. 2. Liver and kidney lipid peroxidation after sulfasalazine administration to rats. SSZ: Sulfasalazine.
Data are shown as Mean±SEM for each group (n=6).
*Indicates significantly different as compared to control group (p<0.05). [a] Indicates significantly different as compared to sulfasalazine-treated group (p<0.05).

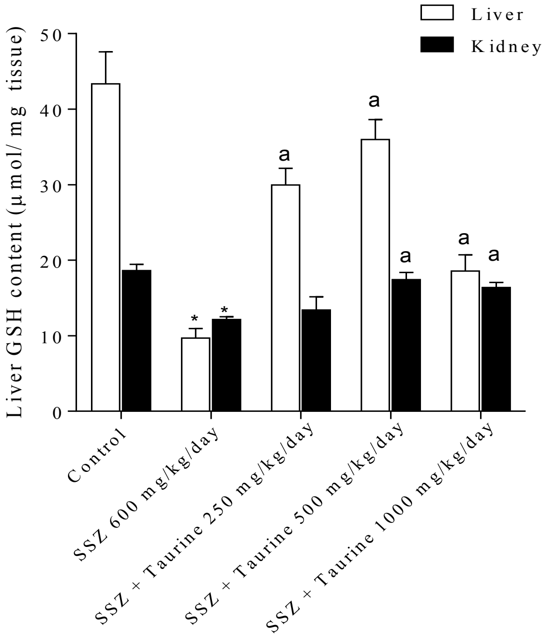

Fig. 3. Tissue glutathione content after sulfasalazine administration. SSZ: Sulfasalazine.
Data are given as Mean±SEM for each group (n=6).
* Indicates significantly lower as compared to control group (p<0.05).
[a] Indicates significantly higher as compared to sulfasalazine-treated group (p<0.05).

lipid peroxidation and protein degradation.

Sulfasalazine is cleaved to sulfapyridine and mesalazine by bacterial azoreductases in the large intestine. Sulfapyridine is almost completely absorbed compared with about 20–30% absorption for mesalazine. About 10-30% of sulfasalazine is also absorbed unchanged from the small intestine.[35] It is not clear that whether the whole molecule of sulfasalazine and/or its intestinal metabolites is responsible for the oxidative stress induction and organ injury induced by this drug. More research on the fate of sulfasalazine and its intestinal metabolites in the body might shed light on the mechanisms of kidney and liver injury in human.

A number of investigations about the antioxidant properties of taurine in the lung,[36,37] heart,[38] kidneys,[39,40] and liver [41,42] have been published. Antioxidant properties and other physiological roles of taurine such as osmoregulation, membrane stabilization and modulation of intracellular calcium levels are well established.[15] In addition to its antioxidant properties, taurine might also be beneficial by increasing the activity of the intracellular antioxidant enzymes including glutathione peroxidase, catalase, and superoxide dismutase.[24,42-44] The protective properties of taurine against sulfasalazine-induced kidney and liver injury might be attributed to its ability to stabilize bio-membranes, scavenging reactive oxygen species, reducing the production of lipid peroxidation end products and finally increasing the activity of cellular defense mechanisms.

Clinical presentation of sulfasalazine-induced renal injury has typically been associated with interstitial nephritis, glomerulonephritis, nephrotic syndrome and acute renal failure.[45,46] Taurine administration counteracted the deleterious effects of sulfasalazine on renal tubular function in our study. Taurine might protect renal system through regulation of blood flow, scavenging reactive oxygen species, cell volume regulation, and immunomodulatory action.[47,48] Taurine might also alter the concentration of the nephrotoxic agents in the kidney.[49] Moreover, it has been reported that taurine alleviated oxidative stress in kidney tissue through protecting vital organelles such as mitochondria.[40]

Taurine is the most abundant amino acid presented in high concentrations in mammalian tissues. Several investigations indicated its safety in human even in very high doses.[50] Hence, these unique properties make it an appro-

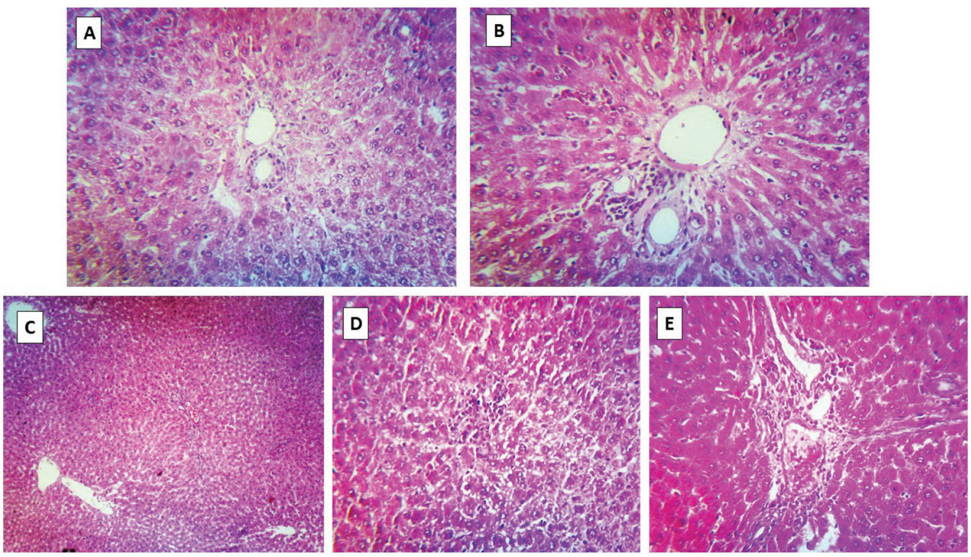

Fig. 4. Liver histopathological changes after sulfasalazine administration to rats (H&E staining). (A) Liver tissue of control animals. (B) Sulfasalazine-treated rats (600 mg/kg/day for 14 consecutive days). Pre-portal inflammation was detected in this group. (C-E) Sulfasalazine + taurine (250, 500 and 1000 mg/kg, respectively). Pre-portal inflammatory cells aggregation was also detected in these groups (C, D, and E).

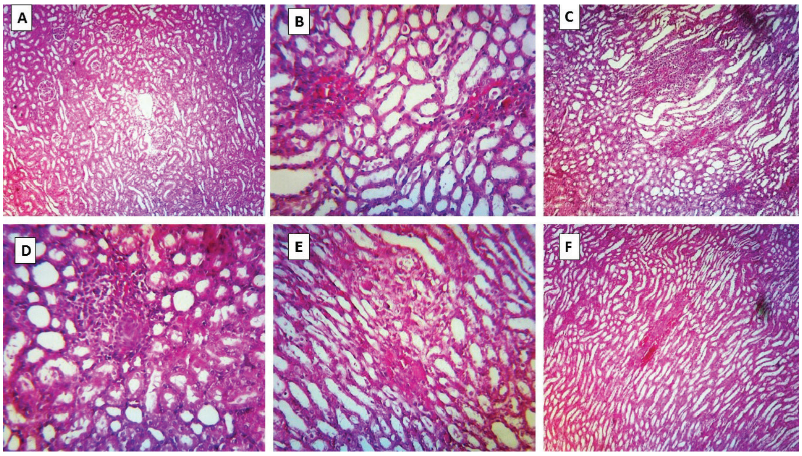

Fig. 5. Kidney histopathological changes in sulfasalazine-treated animals and the effects of taurine administration. (A) photomicrograph of kidney section taken from control (vehicle-treated) rats, depicting normal tubules. (B and C) Sulfasalazine-treated rats, showing marked tubular atrophy, interstitial inflammation, and tubular necrosis. (D-F) Animals received sulfasalazine and taurine (250, 500 and 1000 mg/kg, respectively). Tubular atrophy is detected in these groups, but there is no sign of tubular necrosis.

priate agent to prevent drug-induced organ injury.

Conclusion

In conclusion, we suggest that taurine has a protective role in sulfasalazine-induced renal and liver injury probably by attenuating oxidative stress and its consequences in these organs. Further future investigations are needed to reveal the exact mechanisms of protective properties of taurine against sulfasalazine-induced side effects and finally to clarify the clinical significance of these findings.

Acknowledgments

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Ethical issues

All the experiments were performed in conformity with the guidance for care and use of experimental animals approved by the local ethical committee at Shiraz University of Medical Sciences, Shiraz, Iran (#93-01-36-7612).

Competing interests

There is none to be declared.

Research Highlights

What is current knowledge?

√ Sulfasalazine causes serious adverse reactions including renal and liver injury in patients.

√ Although the precise mechanism of organ injury induced by sulfasalazine is not clear, oxidative stress induction is suspected to be responsible for sulfasalazine adverse effects.

√ Taurine has been proposed to act as an antioxidant, a cell membrane stabilizer, and intracellular ion regulator. Many protective properties are attributed to this amino acid.

What is new here?

√ There is no specific therapeutic option against sulfasalazine-induced renal and hepatic injury.

√ Taurine could be a suitable protective agent against sulfasalazine adverse effects as administration of this amino acid effectively alleviated sulfasalazine-induced kidney and liver injury in this study.

√ The protective properties of taurine are mediated, at least in part, by attenuating oxidative stress in kidney and liver.

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