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# The Effect of Taurine on 2, 4, 6 Trinitrobenzene Sulfonic Acid Induced Colitis

## *2, 4, 6 Trinitrobenzen Sulfonik Asitin İndüklediği Kolit Üzerinde Taurinin Etkisi*

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ÖZET

Amaç: Ülseratif kolit, etiyolojisi bilinmeyen ve kolon ile rektumun iltihabi hastalığıdır. Nötrofil ve aşırı üretilen proinflamatuvar aracılar, sitokinler, araşidonat metobolitleri ve reaktif oksijen metobolitleri patogenezde sorumlu tutulmuştur.

Bu çalışma doku hasarı olan, kolit bir hayvan modelinde oksidatif stres ve antioksidan metabolizması belirteçleri hakkında taurin yönetiminin etkisini değerlendirmek amacıyla yapıldı.

Yöntem: 32 sıçan gruplara ayrıldı. Grup 1 (n=8) trinitrobenzen sülfonik asite bağlı kolit grubu; Grup 2 (n=8) trinitrobenzen sülfonik asite bağlı kolitin intragastrik gavaj yoluyla günde kilogram başına 1 gr taurine verilerek tedavi edildiği grup; Grup 3 (n=8) intragastrik gavaj yoluyla günde yalnızca kilogram başına 1 gr taurine verilen grup; Grup 4 (n=8) her sıçana

ABSTRACT

Objective: Ulcerative colitis is an inflammatory disease of the colon and rectum etiology of which is unknown. Neutrophil and overproduction of proinflammatory mediators including cytokines, arachidonate metabolites, and reactive oxygen metabolites have been implicated in the pathogenesis. The present study was undertaken to evaluate the effect of taurine administration on tissue damage and markers of oxidative stress and antioxidant metabolism in an animal model of colitis.

Methods: Thirty two rats were grouped into: Group 1 (n = 8): Trinitrobenzene sulfonic acid induced colitis group, Group 2 (n = 8): Trinitrobenzene sulfonic acid induced colitis treated with taurine 1g/kg/day via intragastric gavage, Group 3 (n = 8): Taurine alone 1g/kg/day via intragastric gavage treated group, Group 4 (n = 8): Isotonic saline solution 1ml/rat via intragastric

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intragastrik olarak 1 ml izotonik tuz çözeltisinin verildiği kontrol grubu.

Bulgular: Doku malondialdehit düzeyleri, glutatyon düzeyleri; belirlenmesi için immünokimyasal nükleer faktör kappa B ve hem-oksijenaz 1 uygulandı. Çalışmanın sonuçları taurine yönetiminin doku malondialdehit düzeylerini ($p<0.05$) azalttığını buna bağlı, kolit doku hasarını da azalttığını göstermektedir ve kontrol grubuna göre kolon dokularının HO-1 ekspresyonu anlamlı olarak yüksektir. Ayrıca inflamasyon makroskopik ve mikroskopik skorları belirgin nükleer faktör kappa B ($p<0.05$) doku ifadesi olarak da azalmıştır. Beklendiği gibi nükleer faktör kappa B inflamatuvar bir ortamda meydana gelir.

Sonuç: Taurine yönetimi antioksidan mekanizmaların yararlı etkisinde rol aldığı düşünülen glutatyon ve hem-oksijenaz 1doku düzeylerinde artış sağlar.

*Anahtar Kelimeler: Taurin, Kolit, Apoptozis,* NF-KB, HO-1

treated control group.

Results: Tissue levels of malondialdehyde; glutathione levels; as well as immunohistochemical determination of nuclear factor-kappa B and heme oxygenase-1 was performed. The results of the present study suggest that taurine administration significantly reduced the tissue damage in colitis due to the observation that it significantly reduced tissue malondialdehyde levels ($p < 0.05$), and the HO-1 expression of the colonic tissues was found to be significantly higher in group 1 compared to the control group ($p < 0.05$).Furthermore macroscopic and microscopic scores of inflammation were significantly reduced as well as tissue expression of nuclear factor-kappa B ($p < 0.05$). Nuclear factor-kappa B is induced in inflammatory setting as expected.

Conclusion: Taurine administration increased tissue levels of glutathione and heme oxygenase-1 which is suggestive of the possible role of antioxidant mechanisms taking part in its beneficial effect. Taurine seems to have protective effects against colonic damage in Trinitrobenzene sulfonic acid induced colitis through reducing inflammation and enhancing antioxidant metabolism.

*Key words:* Taurine, Colitis, Apoptosis, NF-KB, HO-1

## Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum that is characterized by a set of clinical, endoscopic, and histological features.[1-5] Although the precise etiology of ulcerative colitis remains unknown, it is believed to involve an abnormal host immune response to endogenous or environmental antigens. Microscopically, UC is characterized by massive infiltration of inflammatory cells in the mucosa and submucosa. Activation of these infiltrating cells results in the release of inflammatory mediators.[3,4,6] These mediators include various pro-inflammatory cytokines, chemokines, reactive oxygen species, nitric oxide, and the eicosanoids.[7-10] Since increased lipid peroxidation byproducts and mucosal production of reactive oxygen metabolites have been described in colorectal biopsy specimen of patients with UC, increasing attention has been focused on the role of free radicals in the pathogenesis of UC.[10-15]

Heme oxygenase (HO) is an enzyme that catalyzes the rate-limiting step in heme catabolism. It yields by products of carbon monoxide, free iron, and biliverdin, which all possess free radical scavenging properties[16-18] HO-1 induction has been considered to protect cells against oxidative injuries. The exact role of HO-1 in UC is unclear.[16-19]

NF-κB is a transcription factor that is important for the activation of many inflammatory mediators. Previous studies have found NF-κB to be significantly activated in UC.[20-26]

Taurine is a conditionally essential amino acid that is found either in free or bound form in circulation. In the organism taurine has important physiological functions such as bile salt conjugation, cholesterol excretion, cellular volume regulation, ionic transport.[27] In the clinical setting; taurine is used in the treatment of cardiovascular diseases, epilepsy, macular degeneration, Alzheimer's disease etc. The protective effect of taurine

is associated with anti-inflammatory and antioxidant effects.

The possible contribution of HO-1 to the preventive effect of taurine in mucosal damage in experimental colitis has not been previously evaluated. In the present study, we aimed to investigate the protective effect of taurine against oxidative and inflammatory damage in an experimental model of colitis through investigation of its effects on tissue inflammatory and oxidative markers.

## Materials and Methods

*Design of study groups*

Thirty-two male Wistar-albino rats weighing 250-300 g (Institute of Experimental Medicine and Research, Istanbul University) were used in the study. All animals were housed in wire mesh-bottomed cages under a 12/12-hr light/dark cycle. Rats were kept in a room at a constant temperature 22 ± 2°C. The rats were fed a standard chow diet and water until the experiment. The ethics committee of Istanbul University, Faculty of Medicine approved the study. The animals were divided into four groups as follows: Group 1 (n = 8) Trinitro Benzosulfonic Acid (TNBS) (Sigma Chemical Co, USA) colitis; Group 2 (n = 8) Taurine (Sigma Chemical Co, USA), 1 g/kg/day in to drinking water, for 15 days following TNBS induced colitis; Group 3 (n = 8) Taurine alone, 1 g/kg/day in to drinking water, for 15 days; and Group 4 (n = 8) Isotonic saline solution,1 ml/rat intragastric for 15 days (control group).

*In vivo induction of colitis*

Rats were fasted overnight before induction of colitis and then anesthetized by ether inhalation. In order to induce colitis a 5-French polypropylene catheter was inserted into the rectum until the tip was 10 cm above the anus, and a solution of 80mg/kg TNBS dissolved in 0.25 ml of 50% ethanol was instilled. The rats were then maintained in the supine Trendelenburg position for 15 min.

*Assessment of severity of colitis*

All animals were sacrificed 15 days after TNBS exposure. The distal 12 cm of the colon was excised freed of adherent adipose tissue, rinsed with ice-cold saline, and opened longitudinally. Colon specimens were fixed in 10% buffered formalin for histopathology scoring. Other colonic specimens were saved -80°C for biochemical analysis. The colon was immediately examined macroscopically and damage was scored on a scale of 0–5 as described.[16] In brief : (0) no colonic?damage, (1) hyperemia and no ulcer, (2) linear ulcer and no colonic wall thickening, (3) linear ulcer and colonic wall thickening in one area, (4) colonic ulcer in multiple areas, and (5) major ulcer and?perforation. Rat colons were fixed and paraffin embedded tissue sections were stained with hemotoxylin and eosin (HE). Colonic pathological changes were observed and evaluated by two independent researchers using a modified histopathological score formula.[17]

*Immunohistochemistry of NF-κB and HO-1Expression*

Colon specimens were fixed in 10% buffered formalin. Paraffin blocks prepared from routinely processed specimens were cut into 5-µm slices and deparaffinized. Antigen retrieval was performed after this process. After microwave incubation of the peroxyblock, followed by the ultra V block procedure, primary antibodies were applied (NF-κB neomarker anti-rabbit P50 Ab-2; HO-1: H- 105, rabbit polyclonal IgG; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Following this process, biotinylated secondary antibody, streptovidin peroxidase, and substrate-cromogen (AEC) solution was applied, respectively. Nuclear staining was done with hematoxylin. To allow a quantitative analysis of the munber of NF-κB p65-activated cells in the mucosa, we used an activating score. Each specimen was observed by light microscopy with a x400 magnification after staining of the NF-κB p-65 antibody, and activated cells were counted in three microscopic fields. NF-κB staining intensity was defined as percentages per field and was given scores ranging from 0 to 4; score 0: no staining, 1: <25%, 2: 25–50%, 3: 50–75%, 4: >75%. The HO-1 staining intensity was defined as a percentage and given a score 0: no staining, 1: <25%, 2: 25–50%, 3: 50–75%, 4: >75%.[19]

*Malondialdehyde Assays (MDA)*

The levels of MDA in the colonic tissues were measured to assess lipid peroxidation. Samples of colon, small

intestine, liver and pancreas tissues were homogenized with ice-cold 150 n mol/L potassium chloride for determination of tissue MDA levels. MDA levels were measured spectrophotometrically at 532 nm. Results are expressed as nanomoles of MDA per gram of tissue.[19] In brief MDA is an indirect indicator of lipid peroxidation. At 100°C; the MDA reacts with tiyobarbiturate (TBA) and the product emitts light that can be determined at 532 nm wavelength. 0.2 ml of the colonic tissue homogenates were put in to test tubes and were co incubated with 0.2 ml of 8.1%SDS, 1.5 ml of 20% acetate, 1.5ml of 0.8%TBA and 0.6 ml distilled water. The negative control included the reagents without the homogenate. All the samples and the negative control is incubated in 100°C hot water bath for one hour. Following cooling down 1ml distilled water and 5 ml butanol and pridine were added into each tube and the tubes were centrifuged at 1500 rpm for 10 minutes. The organic phase that had dissociated had been taken for measurement and spectrophotometry at 532 nm wavelength have been performed. The results were calculated with reference to standards and expressed as nmol MDA / mg protein.

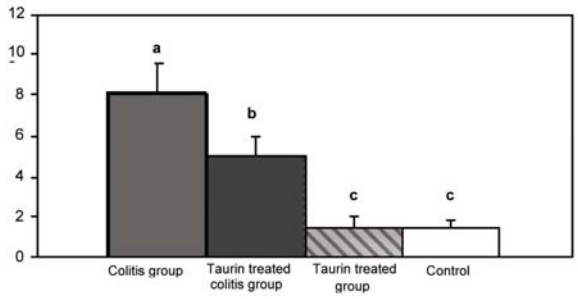


*Figure 1. Mean ± SD colonic microscopic score in the groups. test) a vs b: p < 0.05, a vs c: p < 0.001, b vs c: p < 0.05. (Values have significance according to ANOVA test)*

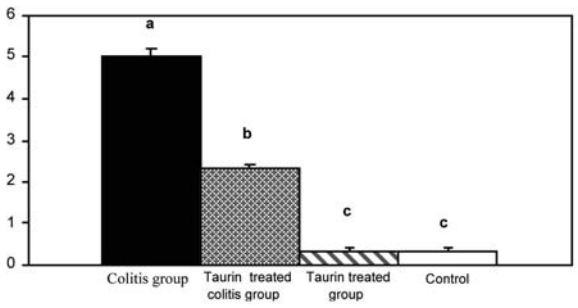


*Figure 2. Mean ± SD colonic macroscopic score in the groups. a vs b: p < 0.05, a vs c: p < 0.001, b vs c: p < 0.05. (Values have significance according to ANOVA test)*

*Glutathione (GSH) Determination*

GSH level in the colonic homogenates was determined by the method proposed by Sedlak and Lindsay.[20] After precipitation with metaphosphoric acid, supernatant was reacted with 5, 5 - dithiobis-2-nitrobenzoic acid (DTNB). Absorbance was read spectrophotometrically at 412 nm.

*Statistical Analysis*

All parameters are expressed as mean ± SD. ANOVA was used for statistical analysis and a p value less than 0.05 was considered to be significant. Statistical analysis was performed using SPSS Statistics 11.0 software (SPSS Inc, IL, USA).

## Results

In TNBS-treated animals, macroscopic and microscopic

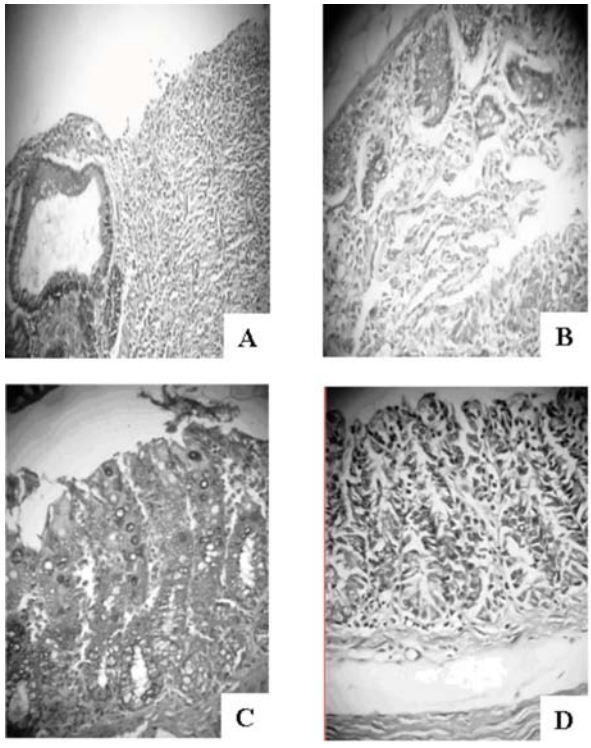


*Figure 3. (A) Colonic mucosa from the TNBS colitis group. Large ulceration (arrow). (B) Colonic mucosa from taurine treated TNBS colitis group. No ulcer area and decreased inflammatory cell infiltration. (C) Normal colonic mucosa from taurine treated group. (D) Normal colonic mucosa from sham control group. (HE; original magnification, *100).*

pathological scores were found to be significantly higher compared to those of the sham group ($p < 0.005$). Treatment with taurine significantly decreased the pathological scores compared to those of TNBS-treated animals ($p < 0.005$) (Fig. 1, 2 and 3).

NF-κB positivity was strongest in the colon of animals in Group 1. Expression was decreased in the taurine treatment group (Fig. 4 - 5).

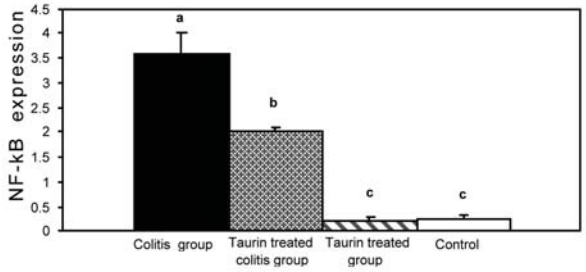


*Figure 4. Mean ± SD ratio of NF-κB expression in the rats colon in the various groups. a vs b: $p < 0.05$, a vs c: $p < 0.05$, b vs c: $p < 0.05$. (Values have significance according to ANOVA test)*

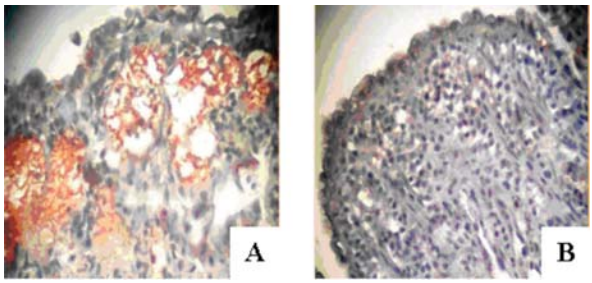


*Figure 5. (A) NF-κB over-expression in the TNBS colitis group (arrow). (Original magnification, x40). (B) NF-κB expression is decreased in colon from the taurin treated TNBS colitis group. (Original magnification, x100).*

The macroscopic colitis scores were found to be significantly increased in TNBS induced animals when compared to the control group ($p < 0.001$). Treatment with taurine (group 2) significantly decreased the score compared to TNBS induced animals (group 1) ($p < 0.001$) (Fig. 1). The microscopic colitis scores were found to be significantly increased in TNBS animals compared to the control group ($p < 0.001$). Treatment with taurine (group 2) significantly decreased the scores when compared to group 1 ($p < 0.001$) (Fig. 2, 3). The HO-1 expression of the colonic tissues was found to be significantly higher in group 1 compared to the control group ($p < 0.05$). Treatment with taurine plus TNBS significantly increased HO-1 expression compared to group 1 ($p < 0.05$). HO-1 expression of the colonic tissues were found to be significantly higher in group 3 compared to the control group ($p < 0.05$) (Fig. 6, 7).

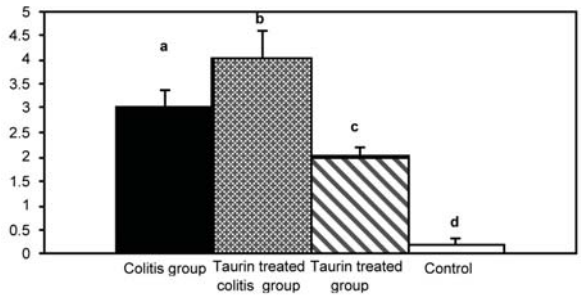


*Figure 6. Mean ratio of heme oxygenase (HO)-1 expression in colonic tissue. a vs b: $p < 0.05$, a vs c: $p < 0.001$, a vs d: $p < 0.001$, b vs c: $p < 0.001$, b vs d: $p < 0.001$, c vs d: $p < 0.001$. (Values have significance according to ANOVA test)*

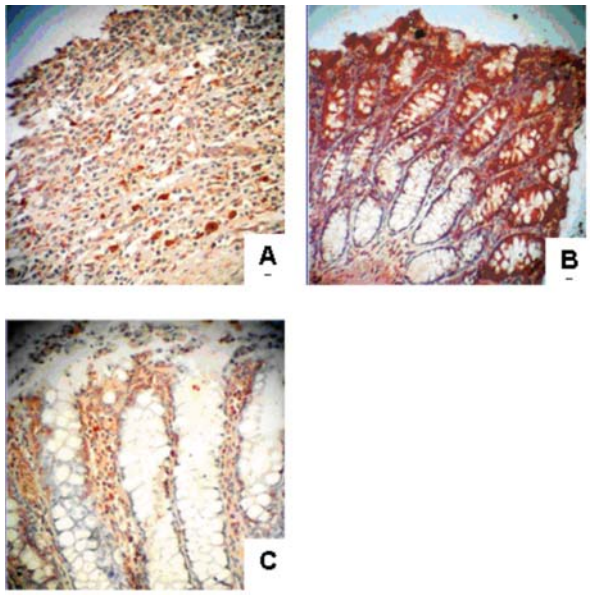


*Figure 7. (A) Colon from the TNBS colitis group showing moderate HO-1 expression (arrows). (B) Colon from the taurine treated TNBS colitis group showing the strong HO-1 expression (arrows). (C) Colon from only taurin treated group showing weak HO-1 expression(arrows).*

MDA levels in colonic tissues were found to be significantly higher in TNBS-treated animals compared to the sham group ($p < 0.005$). Treatment with taurine plus TNBS significantly decreased MDA levels compared to those in TNBS-treated animals ($p < 0.005$) (Figure 8). Glutathione levels in colonic tissues were found to be significantly lower in TNBS-treated animals compared

to the sham group ($p < 0.005$). Treatment with taurine plus TNBS significantly increased GSH levels compared to those in TNBS-treated animals ($p < 0.005$) (Fig. 9).

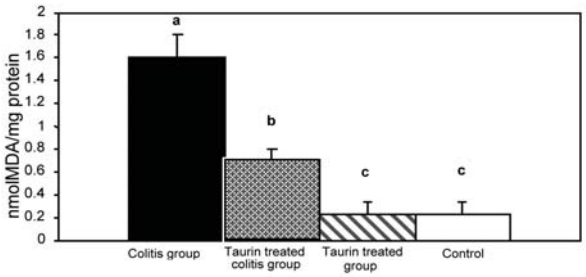


*Figure 8. Mean colonic malondialdehyde (MDA) levels. a vs b: $p < 0.05$, a vs c: $p < 0.001$, b vs c: $p < 0.05$. (Values have significance according to ANOVA test)*

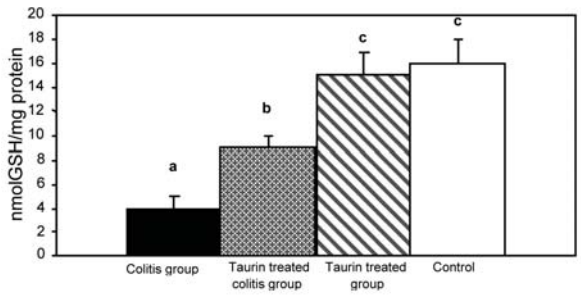


*Figure 9. Mean colonic glutathione (GSH) levels. a vs b: $p < 0.05$, a vs c: $p < 0.001$, b vs c: $p < 0.05$. (Values have significance according to ANOVA test)*

## Discussion

Inflammatory bowel disease, which includes UC and Crohn's disease, is a chronic condition of the intestine with an unknown etiology involving multiple immune, genetic, and environmental factors.[1-3] Many factors have been implicated in the pathogenesis of UC, such as neutrophil infiltration and overproduction of proinflammatory mediators including cytokines, arachidonate metabolites, and reactive oxygen metabolites. Proinflammatory cytokines had significantly high expression and anti-inflammatory cytokines had low expression in the colonic mucosa of UC patients.[4-6,12-26]

The results of the present study suggest that oxidative damage contribute to the development of TNBS-induced colitis as assessed by decreased GSH levels and increased MDA levels, and HO-1 over expression in the colonic tissue. Our results also demonstrate that taurine protects against TNBS-induced colonic damage. The protective effect of taurine is probably associated with induction of HO-1 in the intestinal mucosa with a reduction of tissue inflammation, in addition to the antioxidant effect on colonic tissue.

Since increased lipid peroxidation by products and mucosal production of reactive oxygen mediators were described in colorectal biopsy specimens of patients with UC, increasing attention has been focused on the role of free radicals in the pathogenesis of UC.[6-12] In the present study, colonic MDA levels were found to be significantly higher, whereas colonic GSH levels were found to be significantly lower in the TNBS-treated rats compared to the control group. In addition, demonstration of colonic mucosal damage by microscopic examination in the TNBS-treated rats confirmed colitis-induced inflammation and oxidative damage.

The HO enzyme catalyzes the first and rate-limiting step in heme catabolism. It yields the byproducts of CO, and biliverdin, all of which possess free radical scavenging properties [16,17] Biliverdin is converted to the end product bilirubin by biliverdin reductase. Bilirubin is a very potent natural antioxidant and also a very effective physiological scavenger of superoxides. CO regulates the generation of pro-and anti-inflammatory cytokines. In addition, CO leads to vasodilatation and inhibition of platelet aggregation[16-19] In its free form; iron is oxidatively active. Therefore in cases of oxidative stress elevated iron levels are compensated by elevation of the iron binding protein ferritin. Ferritin is an important molecule which also exerts an antioxidant activity through binding to the iron. HO1 is induced as a result of oxidative stress through the regulation of important transcription factors such as the NRF2 (nuclear factor E2 p45 related factor). HO-1 is an anitoxidant molecule which also induces ferritin. This interaction between HO-1, ferritin and iron has antiapoptotic effect in the organism. We believe that this the mechanism underlying the antiapoptotic effect of HO-1. The protective effect of taurine is probably associated with its site-specific induction of HO-1 in the intestinal mucosa, in addition to the antioxidant effects. The HO-1 levels under the taurin influence are shown in Fig. 4a. NF-KB on the other hand is a nuclear transcription factor that is mainly upregulated in inflammatory reactions. Hence in the taurine treated group; since there is no inflammation in

the colonic tissue the level of NF-KB remained unchanged. Prior studies from our center have concentrated on the effect of taurine on apoptotic mechanisms and tissue damage but the present study has concentrated on the effect of tauine on the markers of inflammation such as NF-KB and also the possible antioxidant mechanism underlying its effect. Three isoforms of HO have been identified. The HO-1 isoform is strongly and rapidly induced by oxidative stress in pathological conditions. In contrast, the HO-2 isoform is constitutive and physiologically expressed. HO-3 is related to HO-2, but is less well characterized. HO-1 induction plays an important role in cellular protection against oxidative injury. HO-1 is highly induced in response to heme, metals, hypoxia, ischemia, inflammation and stress[17-21] Wang *et al*.[22] reported that HO-1 was induced by hemin in colonic tissue damaged by experimental colitis. Prior administration with the HO activity inhibitor mesoporphyrin potentiated the colonic damage. Several research groups have shown that glutamine has an ameliorating effect on inflammation by inducing HO-1 expression in various experimental sepsis and colitis models using a similar methodology to ours.[22,23] In the present study, we found that HO-1 expression was induced with administration of taurine and this improved intestinal damage in TNBS-induced colitis.

The ameliorating effect of taurine has been explained by its antioxidant properties in previous studies, although its mechanism is still unclear. Our aim was to investigate if HO-1 participates in the antioxidative mechanism of taurine. During the inflammatory process, various cytokines are secreted into circulation. NF-κB is activated by proinflammatory cytokines. Previous observations demonstrated that NF-κB activation is significantly elevated in inflammatory bowel disease. In the treatment of patients with inflammatory bowel disease, NF-κB inhibitors such as mesalamine and corticosteroids have been used in different formulations.[24,25] In the present study, NF-κB over expression was detected in the colonic tissue in the TNBS-treated rats. NF-κB is activated by a wide variety of agents, including hydrogen peroxide, ozone, reactive oxygen intermediates, IL-1, TNF-α, bacteria, and viral transcriptions. Once activated, NF-κB transcriptional regulates many cellular genes implicated in early immune, acute phase, and inflammatory responses. The activation of NF-κB depends on the cellular redox potential and a reduced intracellular GSH/oxidized GSH ratio. The amount of activated NF-κB correlates with the degree of mucosal inflammation[26-33] In the present study, NF-κB positivity was strongest in the colonic tissue of TNBS-treated rats. Expression was decreased in the taurine treatment group. Apoptosis is an essential physiological process required for maintenance of tissue homeostasis. Insufficient or excessive cell death can contribute to diseases.[34-42] Taurine was reported to protect cells by scavenging oxygen free radicals by up-regulating the anti-oxidant defenses, by forming chloramines with HOCl, or by binding free metal ions such as Fe2+ by its sulphonic acid group.[28,29] Therefore, increased GSH levels after taurine treatment may play an additional role in decreasing oxidative stress. In our study, a significant decrease in colonic MDA levels and an increase in GSH levels were detected in rats with TNBS-induced colitis following taurine treatment. These protective effects of taurine were found to result from its anti-inflammatory properties and antioxidative activity, as shown by the decrease of MDA level and increase of GSH level.

In conclusion, taurine reduced colonic damage in TNBS induced colitis. The effect of the protection associated with taurine was due to antioxidant, anti-inflammatory and HO-1 induction effects, which were documented by a decrease in NF-κB expression and MDA levels, and a concurrent increase in GSH levels and HO-1 over expression in the colonic tissue.

## Reference


1. Guarner F, Malagelada JR. Role of bacteria in experimental colitis. Best Pract Res Clin Gastroenterol 2003;17:793-04.
2. Kankuri E, Hamalainen M, Hukkanen *et al*. Suppresion of pro-inflamaory cytokine release by selective inhibition of inducible nitric oxide synthase in mucosal explants from patients with ulcerative colitis. Scand J Gastroenterol, 2003;38:186-92.
3. Stokkers P, Hommes D. New cytokine therapeutics for inflammatory bowel disease. Cytokine 2004; 28:167-73.
4. Cho C. Current roles of nitric oxide in gastrointestinal disorders. J Physiol 2001;95:253-6.
5. Danese S, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. Aotuimmun Rev 2004;3:394-400.
6. Shusterman T, Sela S, Cohen H, *et al*. Effect of the antioxidant Mesna (2-mercaptoethane sulfonate) on experimental colitis. Dig Dis Sci 2003;48:1177-85.
7. Sugimoto K, Hanai H, Tozawa K, *et al*. Prevents and amoliorates trinitrobenzene sulfonic acid-induced colitis in mice. Gastroenterology 2002;123:1912-22.
8. Akin ML, Gulluoglu BM, Uluutku H, *et al*. Hyperbaric oxygen improves healing in experimental rat colitis. Undersea Hyperb Med 2002;29:279-85.
9. Andreadou I, Papalois A, Triantafillidis JK, *et al*. Benefical effects of a novel non-steroidal antiinflammatory agent with basic character and antioxidant properties on experimental colitis in rats. Eur J Pharmacol 2002;441:209-14.
10. Woodruff TM, Arumugam TV, Shiels IA, *et al*. A potent and selective inhibitor of group II a secretory phospholipase A2 protects rats from TNBS-induced colitis. Int Immunopharmacol 2005;5:883-92.
11. Pfeiffer CJ, Qiu B, Lam SK. Reduction of colonic mucus by repeated short term stress enhances experimental colitis in rats. J Physiol 2001;95:81-7.
12. Ademoglu E, Erbil Y, Tam B, *et al*. Do vitamin E and selenium have beneficial effects on trinitrobenzenesulfonic acid-induced experimental colitis. Dig Dis. Sci 2004;49:102-8.
13. Jian YT, Mai GF, Wang JD, *et al*. Preventive and therapeutic effects of NF-kappaB inhibitor curcumin in rats colitis induced by trinitrobenzene sulfonic acid. World J Gastroenterol 2005;11:1747-52.
14. Otegbayo JA, Otegbeye FM, Rotimi O. Microscopic colitis syndrome-a review article. J Natl Med Assoc 2005;97:678-82.
15. Kazez A, Demirbag M, Ustundag B, *et al*. The role ofmelatonin in prevention of intestinal ischemia-Reperfusion injury in rats. J Pediatr Surg 2000;35:1444-8.
16. Deshane J, Wright M, Agarwal A. Heme oxygenase-1 expression in disease states. Acta Biochim. Pol 2005;52:273-84.
17. Millar AD, Rampton DS, Chander CL, *et al*. Evaluating the antioxidant potential of new treatments for inflammatory bowel disease using a rat model of colitis. Gut 1996;39:407-15.
18. Otterbein LE, Bach FH, Alam J, *et al*. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. Nat. Med 2000;6: 422-8.
19. Galbraith R. Heme oxygenase: who needs it? Proc. Soc. Exp. Biol. Med 2001;222:299-05.
20. Otterbein LE, Soares MP, Yamashita K, *et al*. Heme oxygenase-1: unleashing the protective properties of heme. Trends Immunol 2003;24:449-55.
21. Katori M, Anselmo DM, Busuttil RW, *et al*. A novel strategy against ischemia and reperfusion injury: cytoprotection with heme oxygenase system. Transpl. Immunol, 2002;9:227-33.
22. Wang WP, Guo X, Koo MW, *et al*. Protective role of heme-oxygenase-1 on trinitrobenzene sulfonic acid-induced colitis in rats. Am. J. Physiol. Gastrointest. Liver Physiol 2001;281:586-94.
23. Attuwaybi BO, Hassoun HT, Zou L, *et al*. Hypothermia protects against gut ischemia / reperfusioninduced impaired intestinal transit by inducing heme oxygenase-1. Surg. Res 2003;115: 48-55.
24. Jobin C, Sartor RB. The I kappa B/NF-kappa B system: a key determinant of mucosal inflammation and protection. Am J Physiol Cell Physiol 2000;278: 451-62.
25. Jobin C, Sartor RB. NF-|B signaling proteins as therapeutic targets for inflammatory bowel diseases. Inflamm. Bowel. Dis 2000;6:206-13.
26. Balkan J, Kanbağli O, Hatipoğlu A, *et al*. Improving effect of dietary taurine supplementation on the oxidative stress and lipid levels in the plasma, liver

and aorta of rabbits fed on a high-cholesterol diet. Biosci Biotechnol Biochem 2002;66:1755-8.
27. Hansen SH. The role of taurine in diabetes and the development of diabetic complications. Diabetes Metab Res Rev 2001;17:330-46.
28. Schaffer S, Azuma J, Takahashi K, *et al*. Why is taurine cytoprotective? Adv Exp Med Biol 2003;526:307-21.
29. OriyanhanW, Yamazaki K, Miwa S, *et al*. Taurine prevents myocardial ischemia/reperfusion-induced oxidative stress and apoptosis in prolonged hypothermic rat heart preservation. Heart Vessels 2005;20:278-85.
30. Chang CK, Llanes S, Schumer W. Inhibitory effect of dimethyl sulfoxide on nuclear factorkappa B activation and intercellular adhesion molecule 1 gene expression in septic rats. J Surg Res 1999;82:294-9.
31. Schmid RM, Adler G. NF-B/Rel/IkB: Implications in gastrointestinal diseases. Gastroenterology 118:1208-26, Springer. Dig Dis Sci 2006;51:1538-45.
32. Akdis CA, Blaser K, Akdis M. Apoptosis in tissue inflammation and allergic disease. Curr Opin Immunol 2000;16:717-23.
33. Jones BA, Gores GJ. Physiology and pathophysiology of apoptosis in epithelial cells of the liver, pancreas, and intestine. Am J Physiol 1997;273:1174-88.
34. Potten CS, Booth C. The role of radiation-induced and spontaneous apoptosis in the homeostasis of the gastrointestinal epithelium: a brief review. Biochem Physiol Biochem Mol Biol 1997;118:473-78.
35. Potten CS,Wilson JW, Booth C. Regulation and significance of apoptosis in the stem cells of the gastrointestinal epithelium. Stem Cells 1997;15:82-93.
36. Sun F, Hamagawa E, Tsutsui C, *et al*. Evaluation of oxidative stress during apoptosis and necrosis caused by D-galactosamine in rat liver. Biochem Pharmacol 2003;65:101-07.
37. Redmond HP, Wang JH, Bouchier-Hayes D. Taurine attenuates nitric oxide- and reactive oxygen intermediate-dependent hepatocyte injury. Arch Surg, 1996;131:1280-88.
38. Franconi F, Di Leo MAS, Bennardini F, *et al*. Is taurine beneficial in reducing risk factors or diabetes mellitus? Neurochem Res 2004;29:143-50.
39. Dogru-Abbasoglu S, Kanbagli Ö, Balkan J, *et al*. The protective effect of taurine against thioacetamide hepatotoxicity of rats. Hum Exp Toxicol 2001;20:23-7.
40. Cetiner M, Sener G, Sehirli AO, *et al*. Taurine protects against methotrexate-induced toxicity and inhibits leucocyte death. Toxicol Appl Pharmacol 2005;209:39-50.
41. Casey RG, Gang C, Joyce M, *et al*. Taurine attenuates acute hyperglycaemiainduced endothelial cell apoptosis, leucocyte–endothelial cell interactions and cardiac dysfunction. J vsc Res 2007;44:31-9.
42. Erbil Y, Girifl M, Abbasoğlu SD, *et al*. Effect of HO-1 on TNBS-induced colitis. Journal of Gastroenterology and Hepatology 2007;22:1852-58.