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ORIGINAL RESEARCH ARTICLE

High-dose taurine exacerbates ulcerative colitis via macrophage activation

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Abstract

While taurine is generally considered beneficial, excessive intake may be harmful under certain conditions. In this study, we examined the effects of dietary taurine on Wistar rats with ulcerative colitis (UC)—a chronic inflammatory disease—induced with 3% dextran sulfate sodium (DSS). Normal rats fed a 10% taurine diet served as the control group, and UC model rats were assigned to the DSS group (standard diet) or taurine-supplemented diets containing 1%, 5%, or 10% taurine (the 1 TAU, 5 TAU, or 10 TAU group). In parallel, primary peritoneal macrophages were stimulated with lipopolysaccharide (LPS) and/or taurine *in vitro*. Control rats gained more weight than all DSS-exposed groups and showed no colonic atrophy or increased inflammatory scores. Among DSS-exposed rats, the 10 TAU group was associated with the greatest body weight loss and the highest disease activity index, whereas colon length did not differ significantly on day 20. Histology revealed epithelial injury and inflammatory infiltration in DSS-exposed groups, with the most pronounced damage in the DSS and 10 TAU groups and comparatively milder injury in the 1 TAU and 5 TAU groups. Serum TNF-α was significantly elevated in the 5 TAU group and showed an increasing trend in the 10 TAU group. *In vitro*, taurine enhanced macrophage activation in an LPS-stimulated context. Overall, very high dietary taurine (10% w/w) was associated with pathological exacerbation and greater histopathologic severity, while 5% taurine showed intermediate, outcome-dependent effects rather than a uniform dose response.

Keywords: Macrophage; Nutrient; Taurine; Ulcerative colitis; Rat; Inflammation

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1. Introduction

Ulcerative colitis (UC) is a chronic and intractable disease characterized by symptoms such as abdominal pain, diarrhea, and hematochezia.[1] The global prevalence of UC is steadily increasing, particularly in Europe and the United States.[2] UC is marked by cycles of relapse and remission, imposing a significant psychological and physical burden on patients. At present, there is no definitive cure for UC, and patients require ongoing medical care, including regular hospital visits and laboratory monitoring. While environmental, genetic, and immunological factors have been implicated in the pathogenesis of UC, the precise mechanisms remain unclear.[3] Among environmental factors, dietary habits play a critical role in disease development. In particular, high-

carbohydrate and high-fat diets have been shown to disrupt the gut microbiota, thereby exacerbating UC symptoms.[4,5] As a result, dietary recommendations for UC emphasize maintaining adequate caloric intake while avoiding excessive consumption of carbohydrates and fats. However, no standardized dietary therapy for UC has been established to date.

Taurine is synthesized from cysteine and methionine primarily in the liver and is one of the most abundant amino acids in the body.[6] It is also found in high concentrations in meat and marine products, while being scarce in plant-based foods.[7] Taurine is known to exhibit antioxidant, anti-inflammatory, and neuroprotective properties, contributing to the maintenance of overall health.[8] However, some studies have reported potential adverse effects of taurine, including elevated blood pressure, an increased risk of atherosclerosis, and reduced platelet counts.[9,10] As such, both beneficial and harmful effects of taurine have been reported, and its influence on specific diseases remains controversial. Several studies have also explored the relationship between taurine and the pathogenesis of UC. In mouse models of UC, taurine has been shown to bind to toll-like receptor 4 (TLR4) and exert anti-inflammatory effects by inhibiting the TLR4/nuclear factor kappa B (NF-κB) signaling pathway.[11] Furthermore, serum taurine levels have been reported to be significantly lower in UC patients than in healthy individuals, particularly during the active phase of the disease.[12] These findings suggest that taurine may have therapeutic potential in the management of UC, based on its reported beneficial effects.

Animal studies are a valuable approach for investigating the effects of taurine on specific diseases. By adding defined amounts of taurine to animal feed or drinking water, its impact on pathological conditions can be assessed. For example, one study reported that supplementing the diet of obese C57BL/6 mice with 5% taurine by weight suppressed appetite and reduced visceral fat accumulation.[13] Another study demonstrated that administering 1.5% taurine in the drinking water of middle-aged mice improved the function of bone, muscle, pancreas, brain, and adipose tissue, thereby extending healthy lifespan.[14] In our previous research, we used a rat model of dextran sulfate sodium (DSS)-induced UC and administered specialized diets containing excess amounts of individual monosaccharides to evaluate their effects on disease progression.[15]

While various environmental factors can influence the outcomes of human studies, these variables are more tightly controlled in animal experiments, allowing for a more precise evaluation of the factor under investigation. Based on this background, we sought to determine whether taurine intake has a beneficial effect on the pathogenesis of experimental UC. In humans, taurine is rarely consumed in isolation, and its potential effects—either therapeutic or harmful—may be masked by interactions with other dietary components. In this study, we supplemented the diets of rats with DSS-induced UC with taurine and evaluated its impact on disease severity. Additionally, we cultured macrophages (MΦ) isolated from the peritoneal cavity of rats and monitored changes in their activity following taurine supplementation in the culture medium.

2. Materials and methods

2.1. Materials

Wild-type Wistar rats (WT, male, 10-week-old, each weighing 220–250 g) were purchased from Shimizu Laboratory Supplies Co., Ltd., Kyoto, Japan. Animals were acclimated for approximately 1 week before the experiment with free access to regular diets (MF, Oriental Yeast Co., Ltd., Tokyo, Japan) and water. During the experiments, animals were housed in individual sawdust-lined plastic cages under controlled temperature (22 °C) and humidity (60%) conditions, with day-night cycles regulated using artificial light (12/12 h). All animal experiments were conducted in accordance with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines and were approved by the Animal Care and Use Committee of Kyoto Tachibana University (approval number: 23-04). In this experiment, the concentration of DSS was set at 3%, and the administration period via drinking water was limited to 10 days to avoid excessive disease severity and prolonged animal suffering. The total experimental period lasted up to 20 days, during which the rats' body weight and general condition were monitored daily. At the end of the study, animals were euthanized following intraperitoneal administration of an anesthetic mixture (0.375 mg/kg medetomidine, 2.0 mg/kg midazolam, and 2.5 mg/kg butorphanol).[16] Under anesthesia, blood was collected via cardiac puncture, after which the hearts were removed, and death was confirmed.

Taurine, DSS salts (molecular weight, 36,000–50,000), 1 % eosin Y solution, and *Escherichia coli* O111:B4-derived lipopolysaccharide (LPS) were purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan). Mayer's hematoxylin solution was purchased from Muto Pure Chemicals Co., Ltd. (Tokyo, Japan). Anti-inducible nitric oxide synthase (iNOS) IgG, The PRO-PREP™ Protein Extraction Solution (Cell/Tissue), interleukin (IL)-6 PicoKine™, and enzyme-linked immunosorbent assay (ELISA) kits for IL-1β, and tumor necrosis factor alpha (TNF-α) were purchased from Cosmo Bio Co., Ltd. (Tokyo, Japan). Tetramethylrhodamine (TRITC)-labeled anti-mouse IgG was purchased from Funakoshi Co.,

Ltd. (Tokyo, Japan). VECTASHIELD Antifade Mounting Medium containing 4',6-diamidino-2-phenylindole (DAPI) was purchased from Vector Laboratories, Inc. (Newark, CA, USA). Clinical thioglycolate medium E-MC17 was supplied by Eiken Chemical Co., Ltd. (Tokyo, Japan). TRIzol reagent, Maxima H Minus cDNA Synthesis Master Mix, PowerUp SYBR Green Master Mix for real-time PCR, and all primers were purchased from Thermo Fisher Scientific (Waltham, MA, USA). A powder diet AIN-93G was purchased from Oriental Yeast Co., Ltd. All other reagents were purchased from Wakenyaku Co., Ltd. (Kyoto, Japan), Nacalai Tesque Co., Ltd. (Kyoto, Japan), and Bio-Rad Laboratories, Inc. (Hercules, CA, USA).

2.2. Protocol for animal experiments

WT rats were assigned to five groups (control, DSS, 1 TAU, 5 TAU, and 10 TAU; $n = 6$ per group). The control group consisted of normal rats fed AIN-93G supplemented with 10% w/w taurine without DSS exposure. The DSS group received standard AIN-93G, and the taurine groups (the 1 TAU, 5 TAU, and 10 TAU groups) received AIN-93G supplemented with 1%, 5%, or 10% w/w taurine, respectively; these four groups were subjected to DSS to induce colitis. During the first 10 days of the experiment, all groups were allowed free access to their assigned diets. To induce experimental UC, distilled water was replaced with a 3% DSS solution from day 11 to day 20 in the DSS and TAU groups, whereas the control group continued to receive distilled water. Throughout the experimental period, body weight, remaining food, and remaining 3% DSS solution were recorded daily for each rat. Disease activity index (DAI) scores were calculated based on the criteria.[17] To summarize the criteria concisely, we assigned a score from 0 to 4 based on weight loss, stool consistency, and the degree of bleeding. On day 20, rats were anesthetized, and blood samples (3 mL per rat) were collected via intracardiac puncture. The entire colon was promptly excised, and its length was measured. Tissues were then fixed in 10% formalin in 0.1 M phosphate buffer (pH 7.4) for histological analysis and paraffin embedding. Protein was extracted from the remaining unfixed tissues as described below.

2.3. Sample preparation for the protein assay

The large intestine removed from each experimental rat was weighed separately. Subsequently, 300 mg of each sample was incubated in 0.5 mL PRO-PREP™ Protein Extraction Solution (cell/tissue) for 20 min at −20 °C, followed by centrifugation (4 °C, 12,000 rpm, 10 min). The resulting supernatants were transferred into polycarbonate tubes (1.5 mL) and stored at −80 °C.

2.4. Microscopic observation of rectal tissues

The inflammatory condition of rectal tissue in each rat was examined under light microscopy. Tissue sections (3 μm-thick) were prepared and stained with hematoxylin and eosin (H&E). Tissue damage was evaluated using histological severity (HIS) scores based on H & E staining, with the extent of damage assessed according to established criteria on a 0–14 scale.[18] To summarize the criteria concisely, we assigned a score ranging from 0 to 14 based on inflammation severity, inflammation extent, crypt damage, and percent involvement. Fluorescent immunohistochemical staining was performed using fluorescently labeled antibodies, as previously described.[19] To detect iNOS expression in rectal tissue, 3 μm-thick sections were incubated overnight at 4 °C in a humidified chamber with anti-iNOS IgG (5 μg/mL), followed by a 1-h incubation at room temperature with TRITC-labeled anti-mouse IgG (5 μg/mL). Stained sections were mounted with VECTASHIELD® Antifade Mounting Medium containing DAPI, and images were acquired using a BIOREVO BZ-9000 microscope (Keyence Co., Ltd., Osaka, Japan). Scale bars (50 μm; green) were embedded in the images using the BZ-9000 imaging software.

2.5. Semi-quantitative analysis of iNOS-positive area

Semi-quantitative analysis of iNOS immunofluorescence was performed using ImageJ/Fiji (NIH). For each image, the region of interest (ROI) was defined as the tissue area, excluding slide background and annotations. The TRITC channel (iNOS) was separated, and an identical threshold was applied across all groups to segment iNOS-positive signals. The percentage of iNOS-positive area (% positive area) was calculated as the area of threshold-positive pixels divided by the total ROI area (excluding background) and expressed as a percentage. All images were acquired using identical microscope settings (objective, exposure time, gain, and illumination) and processed using the same analysis parameters.

2.6. ELISA

The levels of IL-6, IL-1β, and TNF-α in each sample were measured using ELISA kits (Cosmo Bio Co., Ltd, Japan), following the manufacturer's protocols. The absorbance at 450 nm was measured using an iMark™ microplate reader (Bio-Rad Laboratories, Inc.). The cytokine concentrations in the large intestine were determined by conversion per gram of tissue.

2.7. Analysis of rat serum using clinical chemistry assays

Twenty clinical chemistry assays in rat serum were submitted for analysis to the Nagahama Life Science

Laboratory, Oriental Yeast Co., Ltd. (Shiga, Japan). Equal volumes of serum samples from six rats per group were mixed to minimize individual differences. The assay was performed using JCA-BM6050 (JEOL Ltd., Tokyo, Japan) and included measurements of total protein (TP), albumin (ALB), blood glucose (GLU), blood urea nitrogen (BUN), creatinine (CRE), total bilirubin (T-Bil), uric acid (UA), iron (Fe), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), amylase (AMY), creatine kinase (CK), γ-glutamyl transpeptidase (γ-GT), cholinesterase (ChE), total cholesterol (T-CHO), triglyceride (TG), low-density lipoprotein cholesterol-cholesterol (LDL-C), and high-density lipoprotein cholesterol-cholesterol (HDL-C).

2.8. Isolation of peritoneal MΦ from rats

Peritoneal MΦ from WT rats (n = 10) were isolated as previously described.[20] MΦ elicitation was achieved by intraperitoneal injection of 10 mL of 4% thioglycolate in distilled water. After 3 days, the elicited MΦ were collected in a 50 mL plastic tube using 50 mM sterilized phosphate-buffered saline (PBS; buffer A). The tube was then centrifuged at 1,500 rpm for 5 min at 4 °C, and the supernatant was discarded. The cells were resuspended in 17 mM Tris-HCl (pH 7.2) containing 0.83% NH_4Cl to lyse contaminating erythrocytes, and incubated for 5 min at 37 °C. After incubation, the cells were centrifuged again, the supernatant was discarded, and the remaining cells were resuspended in Roswell Park Memorial Institute (RPMI)-1640 medium. A total of 2×10^6 cells were plated in each well of a six-well plate containing an appropriate volume of RPMI-1640 medium and incubated for 2 h in 5% CO_2 at 37 °C. After incubation, non-adherent cells were removed by washing the wells three times with buffer A, and adherent cells were further incubated in the same medium in 5% CO_2 at 37 °C.

2.9. Activation of MΦ and confirmation of their immune response

The MΦ were thoroughly washed with buffer A, resuspended in RPMI-1640 medium supplemented with LPS and/or taurine, and stimulated for 1 or 2 h. The assay conditions were as follows:

(i) N: MΦ incubated in normal RPMI-1640 medium (no stimulation).
(ii) 1h TAU: 10 μg/mL taurine was added to RPMI-1640 medium, and cells were stimulated for 1 h.
(iii) 1h LPS: 10 μg/mL LPS was added to RPMI-1640 medium, and cells were stimulated for 1 h.
(iv) 1h LPS + TAU: Both 10 μg/mL LPS and 10 μg/mL taurine were added to RPMI-1640 medium, and cells were stimulated for 1 h.
(v) 1h LPS → 1h N: After stimulation with 10 μg/mL LPS in RPMI-1640 medium for 1 h, the medium was replaced with normal RPMI-1640 medium and incubated for 1 h.
(vi) 1h LPS → 1h TAU: After stimulation with 10 μg/mL LPS in RPMI-1640 medium for 1 h, the medium was replaced with RPMI-1640 medium containing 10 μg/mL taurine, and cells were incubated for 1 h.

After stimulation under each condition, the MΦ were washed three times with buffer A, and mRNA was extracted from the cells using TRIzol™ reagent. cDNA was then synthesized from the extracted mRNA using the Maxima H Minus cDNA Synthesis Master Mix, following the manufacturer's protocol.

2.10. Real-time PCR

Real-time polymerase chain reaction (PCR) was performed using the StepOnePlus Real-Time PCR System (Thermo Fisher Scientific) as previously described.[19] The mRNA expression levels in each sample were corrected and compared with those of β-actin concentration as the reference gene in the same sample. The results were presented relative to the expression level of the target gene in the N condition of MΦ (ΔΔCT method). The primers used were as follows: IL-1β forward, 5'-CACCTCTCAAGGAGAGCACAGA-3', IL-1β reverse, 5'-ACGGGTTCCATGGTGAAGTC-3' (81 bp); IL-6 forward, 5'-ATATGTTCTCAGGGAGATCTTGGAA-3', IL-6 reverse, 5'-GTGCATCATCGCTGTTCATACA-3' (80 bp); TNF-α forward, 5'-GTGATCGGTCCCAACAAGGA-3', TNF-α reverse, 5'-AGGGTCTGGGCCATGGAA-3' (71 bp); iNOS forward, 5'-GACCAGAAACTGTCTCACCTG-3', iNOS reverse, 5'-CGAACATCGAACGTCTCACA-3' (137 bp), and β-act forward, 5'-TGTGTTGTCCCTGTATGCCTCTG-3', β-act reverse, 5'-ATAGATGGGCACAGTGTGGGTG-3′ (85 bp).

2.11. Statistical analysis

Data are presented as mean ± standard deviation (SD). For comparisons among multiple groups, one-way analysis of variance (ANOVA) was performed first to test for an overall group effect. When the ANOVA was significant, Dunnett's post-hoc test was applied to compare each treatment group with the control group. For outcomes measured over time, a repeated-measures ANOVA (or mixed-effects model) was used as appropriate, followed by Dunnett's test for multiple comparisons against the DSS group (animal experiments) or 1 TAU condition (MΦ experiments). All experiments were repeated five times. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Diet and fluid consumption

We measured daily intake of the diet and drinking fluid during days 11–20, and calculated the average values. There was little difference in diet consumption between groups with and without taurine supplementation (Figure 1A). Similarly, no significant difference in fluid consumption was observed between any of the groups (Figure 1B).

3.2. Changes in body weight and DAI scores

Body weight and DAI scores were recorded daily throughout the experimental period. There were no significant differences in weight gain among the groups up to day 10 (Figure 2A). After day 10, body weight on days 13–20 was significantly lower in the DSS and taurine groups than in the control group (Figure 2A). Rats in the DSS and 1 TAU groups exhibited a gradual weight loss (Figure 2A). In contrast, body weight change suggested

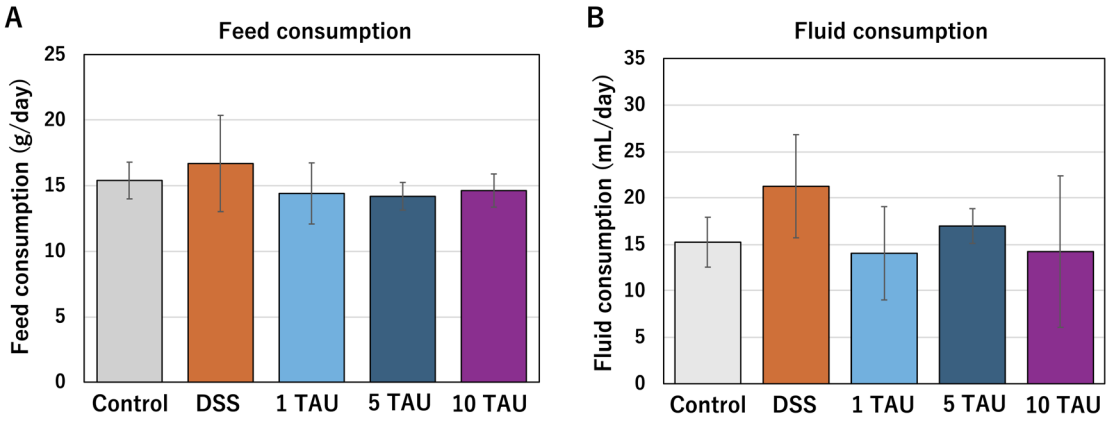

Figure 1. Consumption of feed and drinking fluid. (A) Feed consumption during days 11–20. The y-axis represents daily feed intake (g). (B) Drinking fluid consumption during the days 11–20. The y-axis represents daily drinking fluid intake (mL). The control group consumed distilled water, while the other four groups consumed 3% DSS. Data are presented as mean ± standard deviation (SD). Experimental conditions and color codings are defined as follows: Control group (gray), normal rats fed AIN-93G supplemented with 10% w/w taurine without DSS exposure; DSS group (orange), DSS-induced colitis rats fed standard AIN-93G; 1 TAU group (light blue), DSS-induced colitis rats fed AIN-93G supplemented with 1% w/w taurine; 5 TAU group (dark blue), DSS-induced colitis rats fed AIN-93G supplemented with 5% w/w taurine; 10 TAU group (purple), DSS-induced colitis rats fed AIN-93G supplemented with 10% w/w taurine. $n = 6$ per group. No significant differences were observed among groups in feed consumption (A; one-way ANOVA, $F(4,25) = 0.73$, $p = 0.58$) or fluid consumption during days 11–20 (B; one-way ANOVA, $F(4,25) = 1.12$, $p = 0.37$).

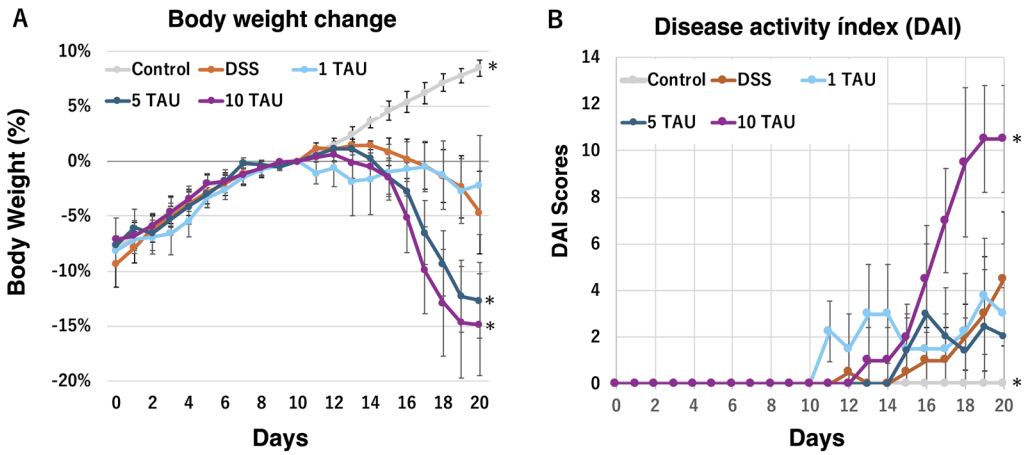

Figure 2. Changes in body weight and disease activity index (DAI) scores. (A) The y-axis indicates the percentage change in body weight. The weight on day 10 was set as the baseline (0%). (B) DAI scores were assessed based on previously established criteria.[17] The y-axis shows DAI scores. The x-axes in both graphs represent days since the start of the experiment. Data are presented as mean ± standard deviation (SD). Refer to the legend in Figure 1 for the experimental conditions and color coding of each group. $n = 6$ per group. *$p < 0.05$ (The DSS group vs the control, 5 TAU, or 10 TAU groups in graph A. The DSS group vs the control or 10 TAU groups in graph B). One-way ANOVA revealed significant differences among groups in body weight change (A; $F(4,25) = 3.21$, $p = 0.029$) and DAI (B; $F(4,25) = 2.98$, $p = 0.038$).

the most pronounced deterioration in the 10 TAU group, whereas the 5 TAU group showed a more modest pattern that did not reach the reduction observed in the 10 TAU group (Figure 2A). DAI scores were assessed based on the criteria.[17] Rats in the 10 TAU group displayed significantly higher DAI scores compared to the other four groups (Figure 2B).

3.3. Changes in rat colon lengths

Colon length was measured on day 20. Although the colon of the control group maintained a slightly longer length, there were no apparent visual differences in colon length among the DSS and taurine groups (Figure 3A). Consistently, mean colon length did not differ significantly in any DSS-exposed group (DSS, 1 TAU, 5 TAU, or 10 TAU) compared with the control group (Figure 3B).

3.4. Microscopic observation and evaluation of colonic inflammation

H & E staining and fluorescent immunohistochemical staining were performed to evaluate colonic mucosal injury and MΦ activation. Compared with the control group, the DSS group already exhibited marked colitis, establishing a strong disease baseline (Figure 4A). Among DSS-treated groups, representative H & E images suggested comparatively milder mucosal damage in the 1 TAU and 5 TAU groups, whereas the 10 TAU group showed epithelial injury and inflammatory infiltration that were comparable in severity to the DSS group (Figure 4A). In fluorescent immunohistochemical staining, iNOS immunoreactivity was minimal in the control group and was detectable in DSS-exposed groups (Figure 4B). Semi-quantitative image analysis demonstrated group-dependent differences in % iNOS-positive area (Figure 4C). Compared with the DSS group, the 10 TAU group showed generally equivalent iNOS expression rates, whereas 1 TAU and 5 TAU showed lower values (Figure 4C). HIS was evaluated on day 20 according to established criteria.[18] Compared with the control group, DSS exposure groups all exhibited increased HIS (Figure 4D). HIS was similarly high in the DSS and 10 TAU groups, whereas lower values were observed in the 1 TAU and 5 TAU groups (Figure 4D).

3.5. Evaluation of serum inflammatory cytokines

Serum TNF-α levels were significantly elevated in the 5 TAU group compared with the DSS group and tended to be increased in the 10 TAU group (Figure 5B). In contrast, serum IL-6 and IL-1β levels did not differ significantly among DSS-treated groups (Figure 5C,D).

3.6. Cytokine concentrations in colon tissues

ELISA was performed to quantify the levels of three inflammatory cytokines in colon tissue from all four groups. Compared with the DSS group, colonic TNF-α and IL-6 levels were slightly higher in the 5 TAU and 10 TAU groups; however, the difference was not statistically significant (Figure 6A,B). Similarly, colonic IL-1β levels were slightly higher in the 5 TAU group, but the differences were also not significant (Figure 6C).

3.7. Clinical chemistry parameters in rat serum

Twenty clinical chemistry parameters were measured in the serum of the experimental rats. Serum ALB and T-CHO, indices of nutritional status, were slightly lower in the 10 TAU group than other groups, whereas AST, ALT, and LDH, indices of liver damage, were higher in the 10 TAU group (Table 1). BUN and CRE, indices of renal damage, were slightly increased in the 1 TAU and 5 TAU groups. Interestingly, CK, a marker of muscle damage, was also increased in the 10 TAU group (Table 1).

Table 1. Results of rat serum clinical chemistry analysis for each group

	Control	DSS	1 TAU	5 TAU	10 TAU
TP (g/dL)	6.4	6.0	6.1	6.2	5.4
ALB (g/dL)	4.5	4.1	4.1	4.2	3.5
GLU (mg/dL)	164	204	197	242	161
BUN (mg/dL)	15.4	16.8	22.2	20.8	22
CRE (mg/dL)	0.28	0.38	0.47	0.45	0.4
T-BIL (mg/dL)	0.05	0.04	0.04	0.04	0.05
UA (mg/dL)	1.6	1.5	2.2	2.8	1.1
Fe (μg/dL)	276	187	185	194	256
AST (IU/L)	92	98	92	112	133
ALT (IU/L)	32	29	25	28	34
ALP (IU/L)	101	116	151	148	102
LDH (IU/L)	462	593	391	528	769
CK (IU/L)	759	813	496	702	1259
ChE (IU/L)	6	6	7	10	6
AMY (IU/L)	1325	2036	1844	1655	1115
r-GT (IU/L)	<3	<3	<3	<3	<3
T-CHO (mg/dL)	66	74	67	81	70
TG (mg/dL)	47	122	66	80	57
LDL-C (mg/dL)	7	8	8	10	10
HDL-C (mg/dL)	29	28	25	30	23

Notes: Control group: rats fed standard powdered diet (AIN-93G); DSS group: rats fed standard AIN-93G; 1 TAU group: rats fed AIN-93G containing 1% w/w taurine; 5 TAU group: rats fed AIN-93G containing 5% w/w taurine; 10 TAU group: rats fed AIN-93G containing 10% w/w taurine.
Abbreviations: ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMY: Amylase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; ChE: Cholinesterase; CK: Creatine kinase; CRE: Creatinine; Fe: Iron; GLU: Glucose; LDH: Lactate dehydrogenase; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; T-Bil: Total bilirubin; T-CHO: Total cholesterol; TG: Triglycerides; TP: Total protein; UA: Uric acid; γ-GT: γ-glutamyltranspeptidase.

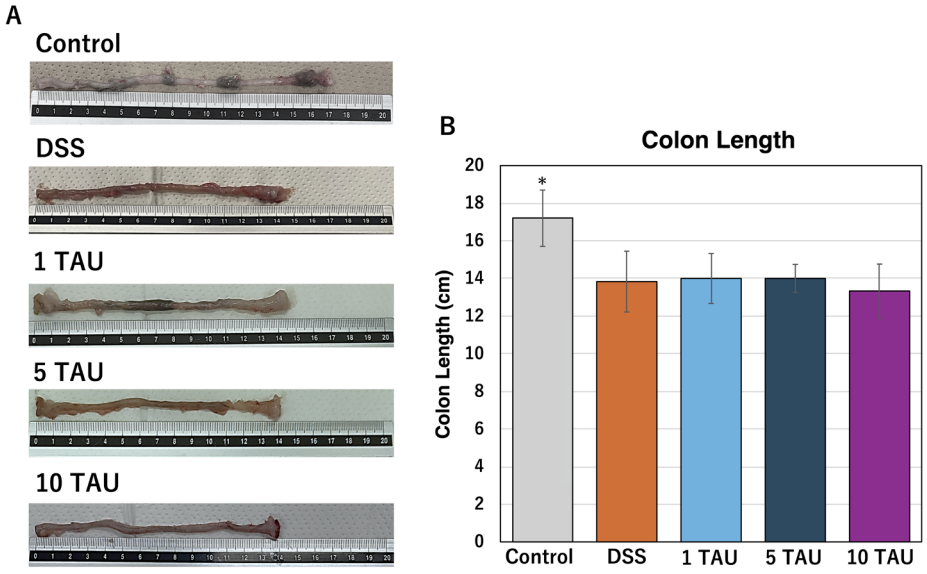

Figure 3. Changes in rat colon length. (A) Representative images of colon tissues from the control, DSS, 1 TAU, 5 TAU, and 10 TAU groups. (B) The y-axis shows colon length (cm) in the control, DSS, 1 TAU, 5 TAU, and 10 TAU groups. Data are presented as mean ± standard deviation (SD). Refer to the legend in Figure 1 for the experimental conditions and color coding of each group. *$p < 0.05$ (The DSS group vs the control group). $n = 6$ per group. One-way ANOVA shows a modest but significant group effect in graph B ($F(4,25) = 2.86$, $p = 0.044$).

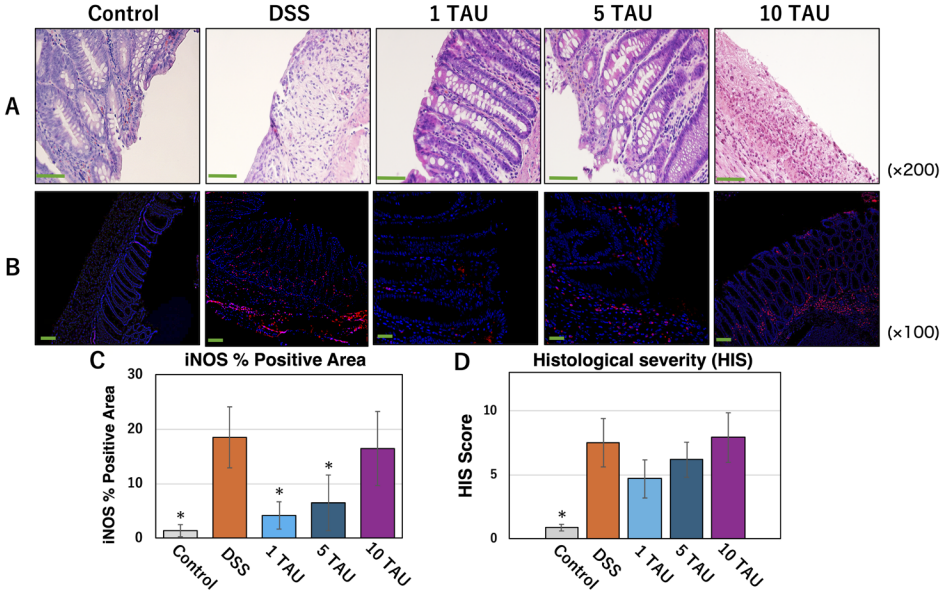

Figure 4. Histological and immunofluorescent assessment of colonic tissues. (A) Representative H & E-stained microscopic images of colonic tissues from the Control, DSS, 1 TAU, 5 TAU, and 10 TAU groups (from left to right). (B) Representative fluorescent immunohistochemical staining images showing activated macrophages (MΦ) in colonic tissues. iNOS on MΦ was labeled with the red fluorescent dye tetramethylrhodamine (TRITC), and nuclei were stained with the blue fluorescent dye 4',6-diamidino-2-phenylindole (DAPI). All images were acquired using a BIOREVO BZ-9000 microscope (Keyence Co., Ltd., Osaka, Japan) at ×200 (H & E-stained images) or ×100 (FICS images) magnification. Scale bars (green) = 50 μm. (C) Semi-quantitative analysis of iNOS signals expressed as % iNOS-positive area based on fluorescent immunohistochemical staining images, quantified using Fiji/ImageJ under identical acquisition and thresholding conditions across groups. (D) HIS on day 20 after the start of the experiment, assessed according to the criteria.[18] The y-axis indicates the HIS for each group. Data are presented as mean ± standard deviation (SD). Refer to the legend in Figure 1 for the experimental conditions and color coding of each group. $n = 6$ per group. *$p < 0.05$ (The DSS group vs the control, 1 TAU, or 5 TAU groups in graph C. The DSS group vs the control group in graph D). One-way ANOVA indicates significant differences among groups in graphs C ($F(4,25) = 3.47$, $p = 0.022$) and D ($F(4,25) = 2.79$, $p = 0.047$).

Abbreviations: H&E: Hematoxylin and eosin; iNOS: Inducible nitric oxide synthase.

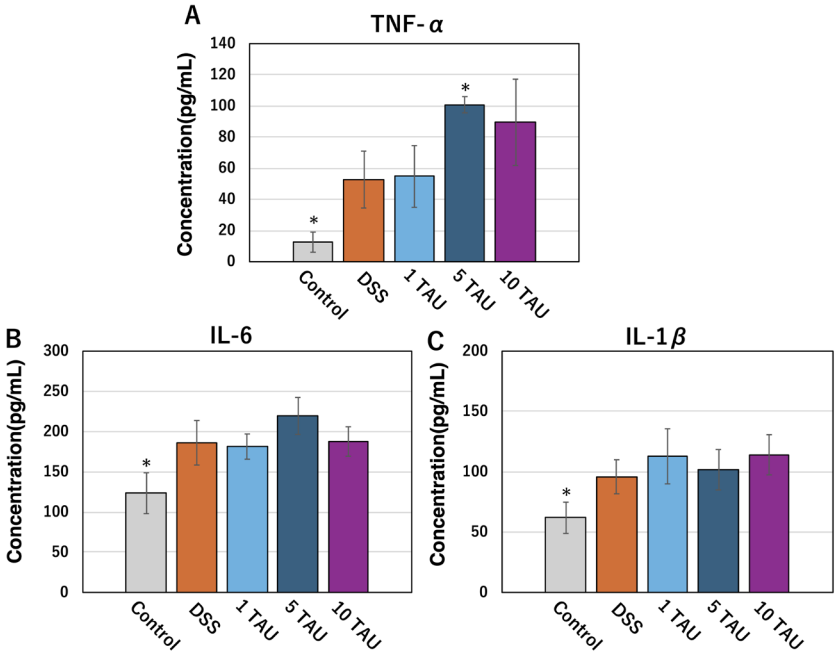

Figure 5. Serum cytokine levels measured by ELISA. (A–C) Serum concentrations of TNF-α, IL-6, and IL-1β (pg/mL) measured by ELISA, respectively. Data are presented as mean ± standard deviation (SD). Refer to the legend in Figure 1 for the experimental conditions and color coding of each group. $n = 6$ per group. $^*p < 0.05$ (The DSS group vs the control or 5 TAU groups in graph A. The DSS group vs the control group in graphs B and C). One-way ANOVA shows significant group effects in graphs A ($F(4,25) = 3.18$, $p = 0.030$), B ($F(4,25) = 2.77$, $p = 0.048$), and C ($F(4,25) = 2.93$, $p = 0.040$).
Abbreviations: IL: Interleukin; TNF-α: Tumor necrosis factor alpha.

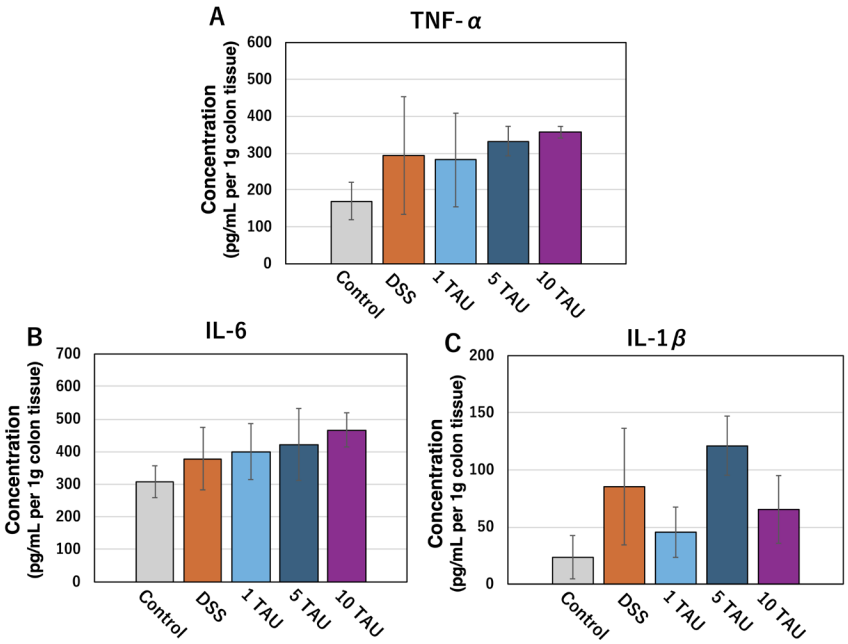

Figure 6. Levels of colonic TNF-α, IL-6, and IL-1β measured by ELISA. The y-axis indicates the concentrations (pg/mL) of colonic cytokines per 1.0 g of colon tissue, as determined by ELISA. Data are presented as mean ± standard deviation (SD). Refer to the legend in Figure 1 for the experimental conditions and color coding of each group. $n = 6$ per group. No significant differences were detected among groups in graphs A–C (one-way ANOVA: A, $F(4,25) = 1.23$, $p = 0.32$; B, $F(4,25) = 0.96$, $p = 0.44$; C, $F(4,25) = 0.71$, $p = 0.59$).
Abbreviations: IL: Interleukin; TNF-α: Tumor necrosis factor alpha.

3.8. iNOS expression in MΦ

The effect of taurine on iNOS activity in rat peritoneal MΦ was examined by fluorescent immunohistochemical staining. A slight induction of iNOS expression was observed under the N and 1h TAU conditions (Figure 7A,B,G), while the iNOS-positive rate was further increased under the 1h LPS condition (Figure 7C,G). In addition, the iNOS expression level under the 1h LPS → 1h N condition was similar to that observed under the N condition (Figure 7A,D,G). Interestingly, iNOS expression was further elevated under the 1h LPS + TAU condition compared to LPS stimulation alone (Figure 7C–E,G). Furthermore, iNOS expression was markedly higher in the 1h LPS → 1h TAU condition compared to the 1h LPS → 1h N condition (Figure 7D,F,G).

3.9. iNOS and inflammatory cytokine mRNA expression in MΦ

The expression levels of iNOS and inflammatory cytokine mRNAs in MΦ were evaluated using real-time PCR. iNOS expression was significantly elevated under the 1h LPS → 1h TAU condition compared to all other conditions (Figure 8A). TNF-α expression was significantly increased under both the 1h LPS + TAU and 1h LPS → 1h TAU conditions compared to the other conditions (Figure 8B). IL-6 expression also showed a significant increase under the 1h LPS + TAU and 1h LPS → 1h TAU conditions (Figure 8C). Similarly, IL-1β expression was significantly higher under the 1h LPS + TAU and 1h LPS → 1h TAU conditions than under the other three conditions (Figure 8D). Notably, the sequential exposure paradigm (1h LPS → 1h TAU) consistently produced stronger induction of iNOS, TNF-α, and IL-1β than co-exposure (1h LPS + TAU) (Figure 8A,B,D).

4. Discussion

In this study, we investigated the impact of taurine-containing diets on the pathogenesis of UC using a DSS-induced rat model. We chose 1%, 5%, and 10% taurine (w/w) to directly compare a putatively tolerable intake level with higher exposures. Based on food-intake–derived conversion, these correspond to approximately 5.6 g/day (1 TAU), 27.5 g/day (5 TAU), and 56.8 g/day (10 TAU) in humans. Importantly, the 1% dose approximates the observed safe level of 6 g/person/day (around 100 mg/

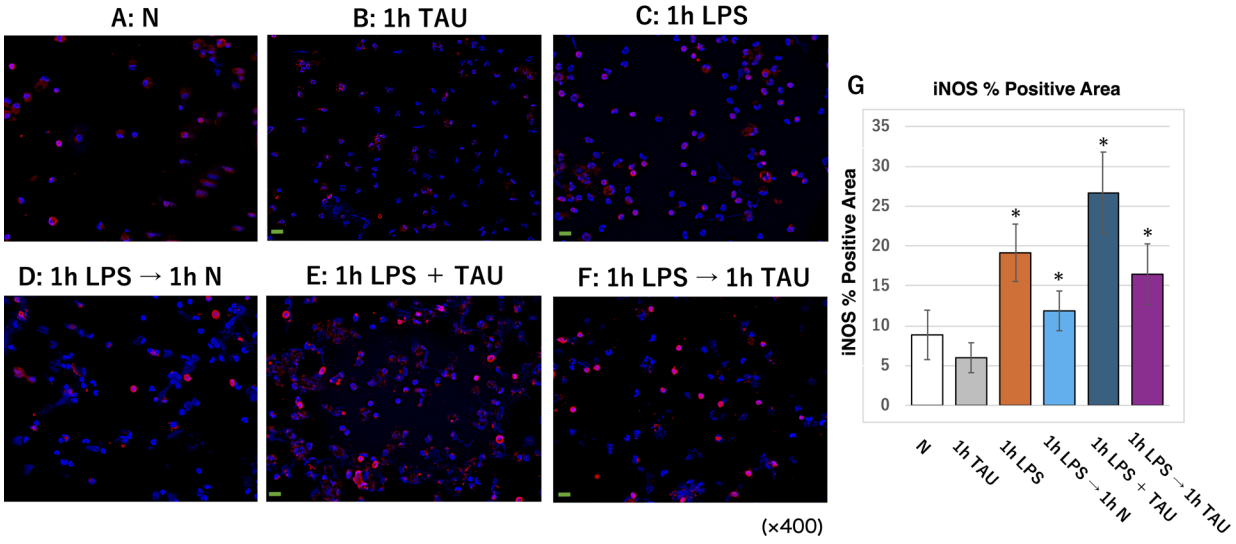

Figure 7. Microscopic fluorescent immunohistochemical staining images showing inducible nitric oxide synthase (iNOS) expression in macrophages. iNOS was detected using tetramethylrhodamine (TRITC)-conjugated antibodies (red), and nuclei were counterstained with DAPI (blue). Panels show representative images from each condition: (A) N, (B) 1h TAU, (C) 1h LPS, (D) 1h LPS → 1h N, (E) 1h LPS + TAU, and (F) 1h LPS → 1h TAU. Images were acquired using a BIOREVO BZ-9000 microscope (Keyence Co., Ltd., Osaka, Japan) at 400× magnification. Scale bars (green) = 50 μm. (G) Semi-quantitative analysis of iNOS signals expressed as iNOS-positive area based on fluorescent immunohistochemical staining images, quantified using Fiji/ImageJ under identical acquisition and thresholding conditions across groups. Data are presented as mean ± standard deviation (SD). Experimental conditions and color codings are defined as follows: N (white), incubated in normal medium for 1 h; 1h TAU (gray), incubated in 10 μg/mL taurine containing medium for 1 h; 1h LPS (orange), incubated in 10 μg/mL LPS containing medium for 1 h; 1h LPS → 1h N (light blue), incubated in medium containing 10 μg/mL LPS for 1 h followed by 1 h incubation in normal medium; 1h LPS + TAU (dark blue), incubated in both 10 μg/mL LPS and 10 μg/mL taurine containing medium for 1 h; 1h LPS → 1h TAU (purple), incubated in medium containing 10 μg/mL LPS for 1 h followed by 1 h incubation in 10 μg/mL taurine containing medium. *$p < 0.05$ (1h TAU condition vs 1h LPS, 1h LPS → 1h N, 1h LPS + TAU, or 1h LPS → 1h TAU conditions). One-way ANOVA reveals a significant effect of stimulation condition in graph G ($F(4,20) = 2.63$, $p = 0.048$).

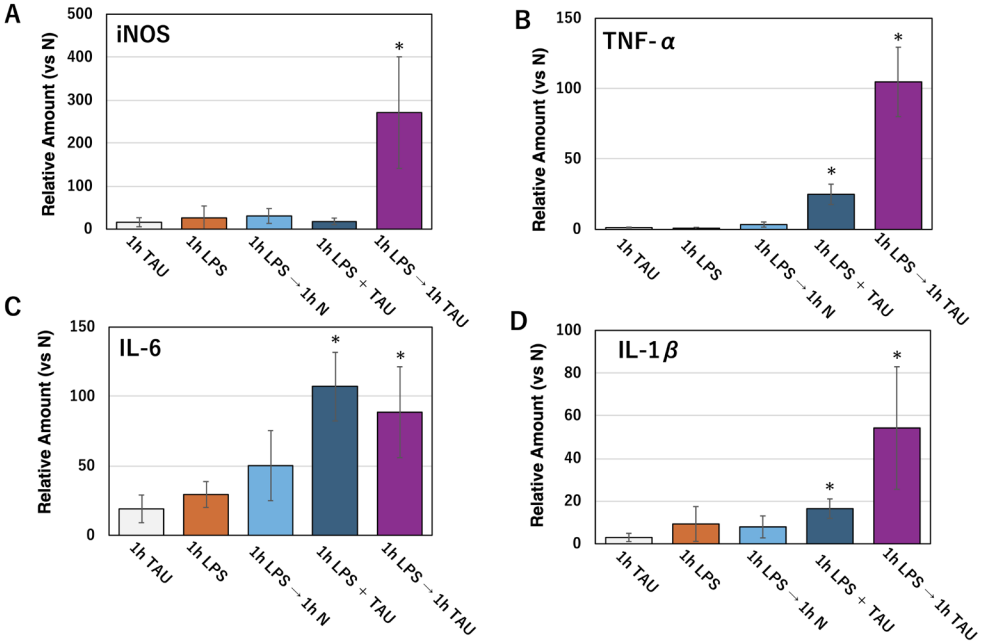

Figure 8. mRNA expression of inducible nitric oxide synthase (iNOS) and inflammatory cytokines in macrophages. Panels (A) to (D) show the mRNA expression levels of iNOS, TNF-α, IL-6, and IL-1β, respectively. The y-axis indicates the expression level relative to that of macrophages under 1h N condition, which is set as 1. Data are presented as mean ± standard deviation (SD). Refer to the legend in Figure 7 for the color coding of each stimulus condition. *$p < 0.05$ (1h TAU condition vs 1h LPS → 1h TAU condition in graph A; 1h TAU condition vs 1h LPS + TAU or 1h LPS → 1h TAU conditions in graphs B–D). One-way ANOVA shows significant effects of stimulation condition in graphs A–D (A, $F(4,20) = 2.95$, $p = 0.045$; B, $F(4,20) = 3.21$, $p = 0.034$; C, $F(4,20) = 2.86$, $p = 0.049$; D, $F(4,20) = 3.08$, $p = 0.039$).

kg/day) reported by the European Food Safety Authority, whereas 10% represents an intentionally high exposure used to test whether excessive taurine intake could be detrimental under active colitis.[21] We acknowledge that intermediate doses (*e.g.*, 2–3% w/w) were not tested in this study; thus, the precise inflection point between neutral and adverse effects cannot be defined here. Future studies using finer dose increments around the clinically relevant range will be needed to identify a more accurate threshold for proinflammatory effects. Colon length was evaluated only at the end of the 20-day protocol. While colon shortening is a commonly used gross marker in DSS colitis, it can reflect not only acute edema and muscle tone but also time-dependent remodeling. Therefore, the current 20-day window may have limited our ability to resolve differences in colon length among DSS-exposed groups. Extending the duration of observation and/or adding additional time points may help determine whether dietary taurine influences the trajectory of colon shortening over a longer course. The DAI and HIS scores are widely adopted as standard assessment tools for DSS colitis.[22] By evaluating these indexes, they provide a robust and multifaceted means of determining the severity of colitis. Then, to address baseline safety, we included a taurine-only control (10% taurine without DSS, the control group), which enabled evaluation of high-dose taurine in the absence of colitis. Notably, rats in this control group did not exhibit a colitis-like phenotype, supporting the interpretation that the detrimental outcomes observed in DSS-exposed animals reflect context-dependent effects rather than nonspecific taurine toxicity. In addition, our data suggest that taurine's impact is strongly dependent on the inflammatory milieu. Because 3% DSS produced a robust inflammatory baseline, the DSS group already showed severe colitis; under this context, 10% taurine resulted in a similarly severe phenotype, indicating no protective effect and a tendency toward a worse clinical course in some readouts. Together, these findings support a context-dependent interaction between excessive taurine intake and ongoing colonic inflammation. Regarding dose–response, our data do not support a simple linear gradient across all readouts. Instead, the 5 TAU group showed an intermediate/partial phenotype—most evident as enhanced body weight loss—whereas the clearest and most consistent aggravation of overall disease severity was observed in the 10 TAU group, including markedly higher DAI and more severe histologic injury. Thus, our findings are best interpreted as dose- and readout-dependent, with a threshold-like deterioration becoming apparent at very high dietary taurine (10% w/w) under DSS-induced

inflammation. A previous report demonstrated that oral taurine administration significantly improved weight loss, diarrhea, intestinal shortening, and inflammatory markers in a DSS-induced mouse model of UC.[23] Thus, while taurine has been reported to exert anti-oxidant and anti-inflammatory effects and is generally considered beneficial in UC, our findings suggest a contrasting mechanism under high-dose conditions.

Potential reasons for the discrepant effects across studies include differences in (i) dose and exposure level, (ii) species (mouse vs rat), and (iii) route/formulation (drinking water vs diet). First, the dose-dependent proinflammatory effect contrasts with earlier studies conducted under low-dose condition, highlighting the importance of considering both disease context and dosage in nutritional interventions. Indeed, taurine concentrations in previous animal studies involving UC typically ranged around 2%,[23,24] whereas our 5–10 w/w % dietary taurine represents a markedly higher intake that may alter epithelial barrier function, thereby modifying host–microbe interactions during active colitis. Second, DSS susceptibility and sulfur–amino acid handling can differ between mice and rats, and the inflammatory "baseline" induced by DSS may therefore interact differently with taurine across species.[25,26] Third, taurine delivered via drinking water can lead to variable daily intake depending on fluid consumption (which itself changes during DSS colitis), whereas diet supplementation provides a more constant exposure relative to food intake; additionally, water-based administration may preferentially reflect short-term luminal exposure while diet-based administration may better model sustained whole-diet intake.[27,28] Collectively, these factors provide plausible explanations for why lower-dose taurine regimens—particularly in mouse studies and/or water-based delivery—have been reported as protective, while a very high taurine load in our rat diet model was not protective and tended to worsen clinical readouts under a robust DSS inflammatory background.

Taurine at approximately 5% of the diet has been used in many studies aimed at treating obesity and hypercholesterolemia.[29, 30] In summary, taurine is commonly used at around 2% in models of inflammation and intestinal disease, while higher doses (>5%) have been applied in studies of metabolic disorders, aging, and oxidative stress. Although typical clinical or dietary exposure to taurine is considered modest and is generally discussed within a range corresponding to low-to-moderate supplementation (often cited as roughly 2% and rarely exceeding 5% in experimental diet equivalents), the 10% taurine condition in this study was intentionally designed to model an extreme exposure scenario. Importantly, the clinical implication is not that routine taurine use is uniformly harmful, but that taurine's impact on colitis may be dose- and context-dependent. An excessive exposure could occur under specific circumstances, such as unsupervised dose escalation of over-the-counter supplements or energy drinks (including concurrent use of multiple taurine-containing products), and continued high intake during active intestinal inflammation when barrier disruption and exposure to microbial products are heightened.[31,32] In addition, formulation-driven regimens (*e.g.*, highly concentrated nutritional protocols or experimental diets) may increase the relative contribution of taurine to total intake. Therefore, our findings highlight the need to define a safety margin for taurine intake specifically under inflammatory conditions and to exercise caution with excessive use during active colitis.

Serum and colonic cytokines were both measured at the terminal time point (day 20), but they reflect different types of information. Serum cytokines represent the overall inflammatory signal circulating in the body, whereas cytokines measured from whole-colon homogenates are an average across the entire colon and may dilute focal mucosal "hot spots" of inflammation. Because we assessed cytokines only at day 20, we could not track how cytokines changed over time during DSS exposure (*e.g.*, early vs. late phases), which should be examined in future studies. At least, serum TNF-α significantly increased in the 5 TAU group and tended to increase in the 10 TAU group. This pattern may reflect a modest systemic inflammatory response during DSS colitis under taurine supplementation, even when endpoint tissue cytokine levels do not show parallel significant changes. We note that serum indicators such as liver (AST, ALT, and CK) and kidney (BUN and CRE) injury markers were altered especially in the 10 TAU group, which may reflect systemic stress and/or extra-intestinal effects at very high taurine intake. Although direct evidence linking altered renal handling of excess taurine to worsening colitis is limited, the kidney is a key regulator of taurine homeostasis, and gut–kidney cross-talk could plausibly contribute to systemic inflammation under extreme exposure. While previous studies have reported that excessive taurine intake can lead to neurotoxicity and hematological disorders,[33,34] our data indicate that multi-organ involvement may also occur. Reports addressing the pathological effects of excessive taurine intake during active intestinal inflammation are rare, making this study highly significant. Because we did not collect liver, kidney, or skeletal muscle tissues, we could not histologically verify organ injury, and thus these findings should be interpreted cautiously. Future studies including organ histopathology and renal/hepatic functional assessments will be needed to

determine whether off-target effects contribute indirectly to colitis severity.

The combination of LPS and taurine appears to activate peritoneal MΦ, as indicated by increased iNOS expression and elevated mRNA levels of inflammatory cytokines (IL-1β, TNF-α, and IL-6). Interestingly, stimulation with taurine alone did not activate MΦ, suggesting that its interaction with LPS was crucial for exacerbating inflammation. iNOS is widely used as a marker of classically activated (M1-like) macrophages in inflammatory settings.[35] Therefore, the increased iNOS-based readouts (tissue iNOS immunofluorescence and *in vitro* induction of iNOS/pro-inflammatory cytokines) support a shift toward a pro-inflammatory MΦ activation state under excessive taurine exposure; however, definitive M1/M2 polarization profiling will require multiparametric approaches such as flow cytometry in future studies. The effects of taurine on MΦ remain controversial. One hypothesis suggests that taurine inhibits M1 polarization, typically associated with proinflammatory activation, when added to cultured MΦ.[36] Another study reported that taurine reduced NF-κB activity in MΦ and suppressed inflammation-related signaling pathways.[37] Globally, few studies have closely examined the interaction between taurine and macrophage activation. From the limited data available, it seems that low concentrations of taurine help modulate MΦ activity, potentially promoting M1-to-M2 repolarization. This may involve regulatory pathways such as NF-κB, STAT1/6 signaling, and mitochondrial homeostasis through mitophagy. Furthermore, taurine's antioxidant and osmoprotective properties may contribute to stabilizing the intracellular environment of MΦ, thereby preventing apoptosis and limiting proinflammatory metabolic shifts. However, little attention has been paid to the possibility that excessive taurine could induce abnormal MΦ activity. Notably, our findings suggest that high-dose taurine, particularly when combined with MΦ activators such as LPS, may enhance proinflammatory responses. Although neutrophils, T cells, and other immune populations are also important to UC pathogenesis, the present study focused on MΦ-related readouts because iNOS-positive MΦ signals were observed in colonic tissue and taurine potentiated activation of freshly isolated primary MΦ *in vitro*. These *in vitro* findings support a direct pro-activating effect of taurine on MΦ under an LPS-stimulated inflammatory context. Nevertheless, taurine may also act indirectly *in vivo* through modulation of epithelial barrier function and/or microbiota-derived metabolites, and the current study did not employ MΦ-targeted loss-of-function approaches (*e.g.*, MΦ depletion or MΦ-specific knockout/knockdown). Therefore, our data support an association between high-dose taurine exposure and MΦ activation signals, while definitive causal attribution will require future MΦ-specific mechanistic studies. An additional insight from our *in vitro* experiments is the apparent importance of exposure sequence. MΦ activation was most pronounced when taurine was applied after LPS priming (1h LPS → 1h TAU), whereas co-treatment with LPS and taurine (1h LPS + TAU) produced a comparatively smaller response. This pattern is consistent with a model in which taurine acts as an enhancer of innate immune signaling once TLR4-driven pathways have been initiated. Given that LPS activates MΦ through TLR4 and downstream NF-κB signaling, one plausible interpretation is that excessive taurine augments the magnitude or persistence of this signaling cascade under inflammatory conditions rather than initiating it *de novo*. In the DSS model, taurine intake and DSS administration are concurrent by design, which was intended to mimic dietary taurine consumption during ongoing barrier disruption and exposure to microbial products. Under such conditions, MΦ *in vivo* are likely repeatedly "primed" by luminal and inflammatory cues; therefore, the post-priming effect observed *in vitro* may still be relevant even without an explicit pre-feeding phase. Nevertheless, we acknowledge that prophylactic versus post-induction taurine exposure could yield different outcomes and may contribute to the non-uniform patterns observed across *in vivo* readouts.

Further studies are needed to determine the optimal taurine dosage and duration, to explore its effects on other immune cells (*e.g.*, T cells, neutrophils), and to investigate its interactions with the gut microbiota. In particular, the impact of taurine on the intestinal microbiota is of great importance, as it is directly linked to the pathogenesis of UC. Emerging evidence indicates that taurine can shape the gut microbial ecosystem and interact with bile acid metabolism.[38,39] Taurine is a major conjugating moiety of bile acids, and microbial bile salt hydrolase–mediated deconjugation can alter both bile acid pools and luminal taurine availability, thereby influencing microbial composition and host inflammatory tone.[38,39] Although gut microbiota was not assessed in the present study, these taurine–bile acid–microbiota interactions may represent an additional, testable axis through which excessive taurine could modulate colitis severity under barrier-disrupted conditions. Another study reported that taurine supplementation reorganized the intestinal microbiota by increasing *Lactobacillus* abundance, altering the bile acid profile in feces, and restoring intestinal homeostasis.[40] In contrast, another study found that taurine is minimally degraded under anaerobic conditions and does not significantly affect microbiota composition, diversity, or short-chain fatty acid production.[41] Taurine is known to conjugate with bile acids (*e.g.*, taurocholic acid) and is

secreted into the intestine.[42] Gut microbes possess bile salt hydrolases that deconjugate these bile acids, releasing free taurine. Certain bacterial species can utilize taurine as a respiratory substrate, leading to sulfide production and energy acquisition.[32] These findings demonstrate that taurine intake is mechanistically intertwined with gut microbial activity. Taurine appears to play a multifaceted role in gut health through its interactions with microbial metabolism, immune modulation, and epithelial barrier integrity. However, its effects are highly dependent on both microbial context and host conditions. Epidemiological studies evaluating the relationship between dietary taurine intake and UC activity in humans could provide valuable insights into its clinical relevance.

The limitation of this study is that taurine exposure was evaluated only within an acute DSS colitis protocol, and thus the long-term safety of low-dose taurine (*e.g.*, 1% w/w) and the possibility of cumulative effects cannot be determined. In addition, because we did not include a recovery/withdrawal phase, it remains unclear whether discontinuation of taurine would attenuate disease severity after DSS-induced inflammation, which should be addressed in future longitudinal studies. Another limitation is that we did not directly assess epithelial cell-death signaling pathways by Western blotting (*e.g.*, TLR4/NF-κB, cleaved caspase-3, GSDMD cleavage, or MLKL phosphorylation); therefore, our data support an association between high-dose taurine and worsened DSS colitis outcomes but do not establish a specific mechanistic pathway. Further *in vitro* investigations, including pathways other than cell death, are considered necessary for our research. In the present study, we examined the effects of taurine in a rat model of UC and demonstrated its pathological consequences when consumed in excess. A major strength of this research lies in its comprehensive approach, which investigated both *in vivo* and *in vitro* effects of high-dose taurine. Moving forward, it is essential to identify the appropriate taurine intake level that maximizes its therapeutic potential while minimizing toxicity. Through continued investigation, we aim to establish dietary guidelines and therapeutic strategies incorporating taurine for UC management, ultimately contributing to the improvement of patient outcomes.

5. Conclusion

Our findings demonstrate that excessive taurine intake exacerbates the severity of UC in DSS-induced rat models, likely through MΦ activation and the subsequent up-regulation of inflammatory cytokines. Although taurine is widely recognized for its anti-oxidant and anti-inflammatory properties, these effects may be reversed in inflammatory conditions when administered at high doses. These results suggest a dose-dependent duality in taurine's immunomodulatory role and underscore the importance of carefully evaluating its use in dietary interventions for UC. Our study enhances the understanding of taurine's complex biological effects and provides a foundation for revising dietary guidelines in the context of UC.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Kohki Okada
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Formal analysis: Shintaro Noborio, Kohki Okada
Investigation: Shintaro Noborio, Kohki Okada
Methodology: Kohki Okada
Project administration: Kohki Okada
Supervision: Kohki Okada
Visualization: All authors
Writing–original draft: Shintaro Noborio
Writing–review & editing: All authors

Ethics approval and consent to participate

The animal experiments were conducted in compliance with the ARRIVE guidelines and were approved by the Animal Care and Use Committee of Kyoto Tachibana University (permission number: 23-04).

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are available upon request from the corresponding author.

References

1. Marks DJ, Segal AW. Innate immunity in inflammatory bowel disease: a disease hypothesis. *J Pathol*. 2008;214(2):260-266.

   doi: 10.1002/path.2291

2. Molodecky NA, Soon IS, Rabi DM, *et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142(1):46–54.

   doi: 10.1053/j.gastro.2011.10.001

3. Sartor RB. Mechanisms of disease: Pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3(7):390–407.

   doi: 10.1038/ncpgasthep0528

4. Zhang Y, Xun, L, Qiao R, *et al.* Advances in research on the role of high carbohydrate diet in the process of inflammatory bowel disease (IBD). *Front Immunol*. 2024;15:1478374.

   doi: 10.3389/fimmu.2024.1478374

5. Chicco F, Magrì S, Cingolani A, et al. Multidimensional Impact of Mediterranean Diet on IBD Patients. *Inflamm Bowel Dis*. 2021;27(1):1–9.

   doi: 10.1093/ibd/izaa097

6. Stipanuk MH. Role of the liver in regulation of body cysteine and taurine levels: a brief review. *Neurochem Res*. 2004;29(1):105-110.

   doi: 10.1023/b:nere.0000010438.40376.c9.

7. Laidlaw SA, Grosvenor M, Kopple JD. The taurine content of common foodstuffs. *JPEN J Parenter Enteral Nutr*. 1990;14(2):183-188.

   doi: 10.1177/0148607190014002183.

8. Schuller-Levis GB, Park E. Taurine: new implications for an old amino acid. *FEMS Microbiol Lett*. 2003;226(2):195-202.

   doi: 10.1016/S0378-1097(03)00611-6.

9. El Idrissi A, Okeke E, Yan X, *et al.* Taurine regulation of blood pressure and vasoactivity. *Adv Exp Med Biol*. 2013;775:407-425.

   doi: 10.1007/978-1-4614-6130-2_31.

10. Pasin F, Porro E, Frattini F, *et al.* Thrombocytopenia induced by a taurine-containing energy drink: an adverse reaction to herbal medicine. *Ital J Med*. 2014;8(4):259-261.

    doi: 10.4081/itjm.2014.466

11. Zheng J, Zhang J, Zhou Y, *et al*. Taurine Alleviates Experimental Colitis by Enhancing Intestinal Barrier Function and Inhibiting Inflammatory Response through TLR4/NF-κB Signaling. *J Agric Food Chem*. 2024;72(21):12119-12129.

    doi: 10.1021/acs.jafc.4c00662

12. Frascatani R, Mattogno A, Iannucci A, *et al.* Reduced Taurine Serum Levels in Inflammatory Bowel Disease. *Nutrients*. 2024;16(11):1593.

    doi: 10.3390/nu16111593.

13. Camargo RL, Batista TM, Ribeiro RA, *et al.* Effects of taurine supplementation upon food intake and central insulin signaling in malnourished mice fed on a high-fat diet. *Adv Exp Med Biol*. 2013;776:93-103.

    doi: 10.1007/978-1-4614-6093-0_10

14. Dawson R, Jr Liu S, Eppler B. Effects of dietary taurine supplementation or deprivation in aged male Fischer 344 rats. *Mech Ageing Dev*. 1999;107(1):73-91.

    doi: 10.1016/s0047-6374(98)00138-9.

15. Okada K, Matsuo K, Amada M, *et al.* Excessive glucose and fructose intake aggravates the pathogenesis of rat experimental colitis. *Gastrointest Disord*. 2023;5(4):474-486.

    doi: 10.3390/gidisord5040039

16. Batbold D, Shinoda M, Honda K, *et al*. Macrophages in trigeminal ganglion contribute to ectopic mechanical hypersensitivity following inferior alveolar nerve injury in rats. *J Neuroinflammation*. 2017;14(1):249.

    doi: 10.1186/s12974-017-1022-3

17. Cooper HS, Murthy SN, Shah RS, *et al.* Clinicopathologic study of dextran sulfate sodium experimental murine colitis. *Lab Invest*. 1933;69(2):238-249.

18. Williams KL, Fuller CR, Dieleman LA, *et al.* Enhanced survival and mucosal repair after dextran sodium sulfate-induced colitis in transgenic mice that overexpress growth hormone. *Gastroenterology*. 2001;120(4):925-937.

    doi: 10.1053/gast.2001.22470

19. Matsuo K, Ikemoto M, Okada K. Intraperitoneal Administration of S100A8 Ameliorates Experimental Acute Colitis in Rats. *Biology*. 2024;13(11):916.

    doi: 10.3390/biology13110916

20. Yoshino T, Nakase H, Honzawa Y, *et al.* Immunosuppressive effects of tacrolimus on macrophages ameliorate experimental colitis. *Inflamm Bowel Dis*. 2010;16(12):2022-2033.

    doi: 10.1002/ibd.21318

21. European Food Safety Authority (EFSA). Scientific Opinion on the safety and efficacy of taurine as a feed additive for all animal species. *EFSA J*. 2012;10(6):2736.

    doi: 10.2903/j.efsa.2012.2736

22. Yang C, Merlin D. Unveiling Colitis: A Journey through the Dextran Sodium Sulfate-induced Model. *Inflamm Bowel Dis*. 2024;30(5):844-853.

    doi: 10.1093/ibd/izad312.

23. Shimizu M, Zhao Z, Ishimoto Y, *et al*. Dietary taurine attenuates dextran sulfate sodium (DSS)-induced experimental colitis in mice. *Adv Exp Med Biol*. 2010;643:265-271.

doi: 10.1007/978-0-387-75681-3_27.

24. Pérez-Hernández E, Pastrana-Carballo JJ, Gómez-Chávez F, *et al.* A Key Metabolic Regulator of Bone and Cartilage Health. *Endocrinol Metab*. 2022;37(4):559-574.

doi: 10.3803/EnM.2022.1443

25. Perše M, Cerar A. Dextran sodium sulphate colitis mouse model: traps and tricks. *J Biomed Biotechnol*. 2012;2012:718617.

doi: 10.1155/2012/718617

26. Adamkova P, Hradicka P, Kupcova Skalnikova H, *et al*. Dextran Sulphate Sodium Acute Colitis Rat Model: A Suitable Tool for Advancing Our Understanding of Immune and Microbial Mechanisms in the Pathogenesis of Inflammatory Bowel Disease. *Vet Sci*. 2022;9(5):238.

doi: 10.3390/vetsci9050238

27. Hassan AM, Jain P, Reichmann F, *et al.* Repeated predictable stress causes resilience against colitis-induced behavioral changes in mice. *Front Behav Neurosci*. 2014;8:386.

doi: 10.3389/fnbeh.2014.00386

28. Hamdani G, Gabet Y, Rachmilewitz D, *et al.* Dextran sodium sulfate-induced colitis causes rapid bone loss in mice. *Bone*. 2008;43(5):945-950.

doi: 10.1016/j.bone.2008.06.018

29. Wang Z, Ohata Y, Watanabe Y, *et al*. Taurine Improves Lipid Metabolism and Increases Resistance to Oxidative Stress. *J Nutr Sci Vitaminol*. 2020;66(4):347-356.

doi: 10.3177/jnsv.66.347

30. Song Q, Kobayashi S, Kataoka Y, *et al.* Direct Molecular Action of Taurine on Hepatic Gene Expression Associated with the Amelioration of Hypercholesterolemia in Rats. *Antioxidants*. 2024;13(8):990.

doi: 10.3390/antiox13080990

31. Curran CP, Marczinski CA. Taurine, caffeine, and energy drinks: Reviewing the risks to the adolescent brain. *Birth Defects Res*. 2017;109(20):1640-1648.

doi: 10.1002/bdr2.1177

32. Candelli M, Franza L, Pignataro G, *et al*. Interaction between lipopolysaccharide and gut microbiota in inflammatory bowel diseases. *Int J Mol Sci*. 2021;22(12):6242.

doi: 10.3390/ijms22126242

33. Gupte R, Christian S, Keselman P, *et al.* Evaluation of taurine neuroprotection in aged rats with traumatic brain injury. *Brain Imaging Behav*. 2019;13(2):461-471.

doi: 10.1007/s11682-018-9865-5

34. Piccioni A, Covino M, Zanza C, *et al.* Energy drinks: a narrative review of their physiological and pathological effects. *Intern Med J*. 2021;51(5):636-646.

doi: 10.1111/imj.14881

35. Orecchioni M, Ghosheh Y, Pramod AB, *et al*. Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. Alternatively Activated Macrophages. *Front Immunol*. 2019;10:1084.

doi: 10.3389/fimmu.2019.01084

36. Meng L, Lu C, Wu B, *et al.* Taurine Antagonizes Macrophages M1 Polarization by Mitophagy-Glycolysis Switch Blockage via Dragging SAM-PP2Ac Transmethylation. *Front Immunol.* 2021;12:648913.

doi: 10.3389/fimmu.2021.648913

37. Prideaux M, Kitase Y, Kimble M, *et al.* Taurine, an osteocyte metabolite, protects against oxidative stress-induced cell death and decreases inhibitors of the Wnt/β-catenin signaling pathway. *Bone*. 2020;137:115374.

doi: 10.1016/j.bone.2020.115374

38. Qian W, Li M, Yu L, *et al*. Effects of Taurine on Gut Microbiota Homeostasis: An Evaluation Based on Two Models of Gut Dysbiosis. *Biomedicine*s. 2023;11(4):1048.

doi: 10.3390/biomedicines11041048

39. Duszka K. Versatile Triad Alliance: Bile Acid, Taurine and Microbiota. *Cells*. 2022;11(15):2337.

doi: 10.3390/cells11152337.

40. Cui C, Song H, Han Y, *et al.* Gut microbiota-associated taurine metabolism dysregulation in a mouse model of Parkinson's disease. *mSphere*. 2023;8(6):e0043123.

doi: 10.1128/msphere.00431-23

41. Sasaki K, Sasaki D, Okai N, *et al.* Taurine does not affect the composition, diversity, or metabolism of human colonic microbiota simulated in a single-batch fermentation system. *PLoS One*. 2017;12(7):e0180991.

doi: 10.1371/journal.pone.0180991

42. Mendes LF, Gaspar VM, Conde TA, *et al.* Flavonoid-mediated immunomodulation of human macrophages involves key metabolites and metabolic pathways. *Sci Rep*. 2019;9(1):14906.

doi: 10.1038/s41598-019-51113-z