Effect of Radiation on the Expression of Taurine Transporter in the Intestine of Mouse

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Abstract There has been a growing interest on the effects of radiation since the Fukushima nuclear power plant accident of 2011. Taurine has been reported to have a radioprotective effect in irradiated mice. However, the detailed mechanism of this radioprotective effect is still awaiting clarification. The aim of this study was to investigation how radiation affects the expression of taurine and to shed light on the mechanism accounting for radioprotective and radiation mitigating effect. Six-week-old male mice were randomly divided into two groups: IR group (7 Gy irradiation) and IR + Tau group (7 Gy irradiation + taurine 3000 mg/kg/day). We examined the survival rate, the expression of taurine and taurine transporter in the small intestine and the urinary taurine concentration. In this study, no statistically significant difference was found in the survival rate between IR Group and IR + Tau Group. Three days and 7 days after irradiation, the urinary taurine concentration of IR + Tau group increased more than that of IR group. Three days and 10 days after irradiation, the expression of taurine and taurine transporter in the small intestine of IR group and IR + Tau group decreased more than that of normal small intestine. It is reported that radiation exposure increases the urinary taurine concentration. We found that the radiation exposure decreases the expression of the taurine transporter in the small intestine of mouse. This finding suggests that a decrease in the expression of the taurine transporter promotes the release of taurine from the tissue into the urine.

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Keywords Radiation • Taurine transporter • Intestine • Oxidation • Inflammation

Abbreviations

IR	X-irradiation
ROS	Reactive oxygen species
Tau	Taurine

1 Introduction

The impact of damage by ionizing radiation exposure in both humans and mice is well known. Radiation generates reactive oxygen species (ROS), free radicals such the hydrogen radical (H^+) and hydroxyl radical (HO^-) in irradiated cells. The free radicals induce injury to living cells DNA (Rostami et al. 2016). Radioprotective agents can offer protection through an ability to remove free radicals. Radioprotectors have been studied for their effect to reduce the cell damage of free radicals in normal tissues for a long time (Weiss and Landauer 2009; Poggi et al. 2001). However, several radioprotectors do not protect irradiated cells when administered after a radiation exposure (Singh et al. 2012; Grebeniuk et al. 2012; Ciorba et al. 2012). This finding suggests that prevention of radiation-induced cellular damages requires the radioprotector to present at the time of irradiation (Grdina et al. 2002; Gu et al. 2000). Unexpected exposure to radiation due to a nuclear plant accident is a common cause of accidental exposure to radiation and one that requires the use of agents that will reduce injury to normal tissue as a result of exposure to radiation. In this case, it is expected that the agent used will accelerate either the recovery from or repair of the radiation injury (Singh et al. 2013). Research on the radioprotective effect of taurine has been carried out since the 1960s (Sugahara et al. 1969). Taurine (2-aminoethanesulfonic acid) is a major intracellular amino acid possessing several important effects, including antioxidant and anti-inflammatory ones (Oliveira et al. 2010; Ma et al. 2010; Kato et al. 2015). Taurine appears to be an attractive candidate for use as a radioprotectors and as a radiation mitigators but at the present time it is not known how it protects against radiation induced cell damage. It is reported that taurine is taken up by cells via taurine transporter (Kwon and Handler 1995). Since reduction of radiation induced cell damage by taurine might be associated with the expression of taurine transporter, it appeared of interest to investigate the expression of the taurine transporter after a radiation exposure. The purpose of this communication is to report that a radiation exposure affects the expression of the taurine transporter in the small intestine of the mouse.

2 Methods

2.1 Animals and Drug Administration

Male ICR mice 6-weeks-old, weighing 26–28 g, were obtained from Japan SLC (Shizuoka, Japan) and handled according to Guidelines for the Regulation of Animals, as provided by animal ethics committee of Suzuka University of Medical Science (Suzuka, Mie-ken, Japan). The animals were maintained in a controlled room at 22 ± 3 °C with a relative humidity of 65 ± 5% and a 12-h light/dark cycle (08:00–20:00). 3000 mg/kg b.w. per day of taurine was given orally by dissolving it in the drinking water to each mouse. Taurine was administered 30 min after irradiation.

2.2 Irradiation

All irradiation experiments were conducted at the X-radiation facility of Suzuka University of Medical Science (Suzuka, Mie-ken, Japan). Mice were irradiated in well ventilated boxes (five mice in each box) to 7 Gy whole body irradiation at a dose rate of 0.331 Gy/min at 200 kV and 9 mA (Phillips MG226, Tokyo, Japan). The beam was filtered through a 0.2 mm copper and 1 mm aluminum board. After irradiation, the mice were returned to their cages and maintained on food and water on an ad libitum basis.

2.3 Animal Groups

The mice were randomly divided into two groups of nine each: IR: 7 Gy whole body X-irradiation and IR + Tau: 3000 mg/kg b.w. per day of taurine after 7 Gy whole body X-irradiation.

2.4 Survival Studies

Two groups of five mice each were used in the experiments. Mice were exposed whole body X-irradiation (7 Gy/mouse). The mice were randomly divided into two groups: IR group (7 Gy irradiation) and IR + Tau group (7 Gy irradiation + taurine 3000 mg/kg b.w. per day). Survival and apparent behavioral deficit of these mice were monitored for a period of 13 days.

2.5 Measurement of Peripheral Blood Lymphocytes

Two groups of nine mice each were used in the experiments. Mice were exposed whole body X-irradiation (7 Gy/mouse). Mice were randomly divided into two groups: IR group and IR + Tau group. Peripheral blood was collected with a capillary tube from the tail vein and then counted lymphocytes with an automated blood cell counter (Celltac-α MEK-6318, Nippon Koden INC, Japan).

2.6 Measurement of Urinary Taurine Concentration

Three mice from each group were killed on days 3 and 10 and their urine collected in 1.5 ml Eppendorf tubes through a needle inserted into the bladder. Samples were frozen at −80 °C immediately after they were collected. The urine taurine concentration was measured by a photometric method based on the dinitrophenylation of the sample followed by chloroform extraction as described by Wilbraham et al. (1971).

2.7 Immunohistochemical Studies

Mice were exposed to 7 Gy of radiation. Three mice from each group were killed on days 3, 7 and 10 for the immunochemical analysis of their small intestines. Small intestines were isolated and fixed in 37% paraformaldehyde overnight and embedded in paraffin. Then, 7 μm-thick paraffin sections were stained with hematoxylin and eosin (H&E). Rabbit taurine-specific antibodies was prepared essentially as described previously (Ma et al. 1994). Taurine transporter (TauT) antibody (SC6A6) was obtained from EnoGene (Tokyo, Japan). Taurine and taurine transporter antibodies immunoreactivities in the intestine sections of mice were observed by a peroxidase anti-peroxidase (PAP) method study. Briefly, paraffin sections (6 μm in thickness) were incubated with rabbit polyclonal anti-taurine antibody (2 μg/ml), anti-taurine transporter antibody (2 μg/ml) overnight at room temperature, respectively. Then, the sections were incubated for 2 h with goat antibody against rabbit IgG (1:200), and were followed by peroxidase anti-peroxidase complex (1:200) for 2 h. The sections that had been treated with first and second antibodies were incubated for 10 min at RT with 3, 3′-diaminobenzidine tetrahydrochloride as chromogen, which had been freshly prepared as a solution of 20 mg in 100 ml PBS that contained 0.01% H_2O_2. Images of tissue sections were captured using an Olympus optical microscope (Olympus Corp., Tokyo, Japan).

2.8 Statistic Analysis

The comparison of means was performed by *t-test* for two-group comparisons. The survival curve analysis was assessed by log-rank test. Each value was expressed as the mean ± SEM. For all tests, significance was accepted when $P < 0.05$.

3 Results

3.1 Taurine Administration Effect of After X-Irradiation in Mouse

The effect of taurine on the survival rate of mice with whole body X-irradiation (7 Gy/mouse) are shown in Fig. 1. The survival rate was found not to be significantly different the between IR Group and IR + Tau Group. The effect of radiation on the peripheral blood lymphocytes of mice are shown in Fig. 2. Taurine was administered 30 min after irradiation. After 7 Gy irradiation, mice exhibited a considerable decrease in the number of lymphocytes. There was no effect on the recovery of lymphocytes on 3 and 7 days. However, we observed early recovery of lymphocytes from the IR + Tau group in 10 days. The effect of radiation on the urinary taurine concentration of mice is shown in Fig. 3. The urinary taurine concentration of the IR + Tau group increased more than that of IR group.

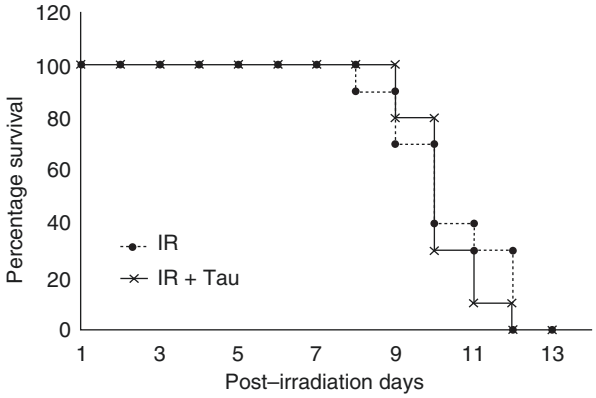

Fig. 1 The effects of the administration of taurine and of irradiation on survival using a 13-day survival curve. Male ICR mice (n = 10) underwent a whole body X-ray radiation (7 Gy/mouse). 3000 mg/kg b.w. per day of taurine was given orally to IR + Tau group. Taurine was administered 30 min after irradiation. Data are shown as the mean ± SE. No statistically significant difference was found in survival rate between IR group and IR + Tau group

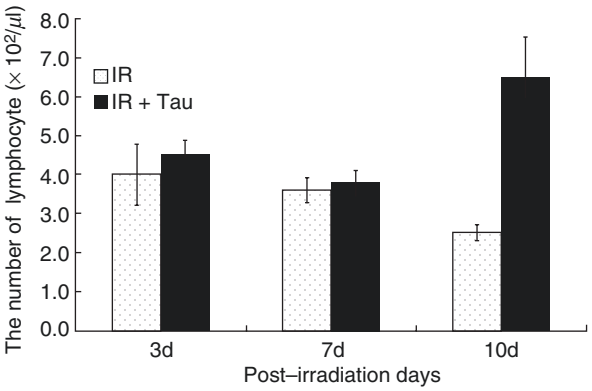

Fig. 2 The effects of the administration of taurine and irradiation on lymphocytes were analyzed using an automated blood cell counter. Male ICR mice (n = 9) were exposed whole body X-irradiation (7 Gy/mouse). 3000 mg/kg b.w. per day of taurine was given orally by dissolving it in the drinking water to IR + Tau group. Taurine was administered 30 min after irradiation. Data are shown as the mean ± SE. Ten days after irradiation, the number of lymphocytes of IR + Tau group increased more than that of IR group

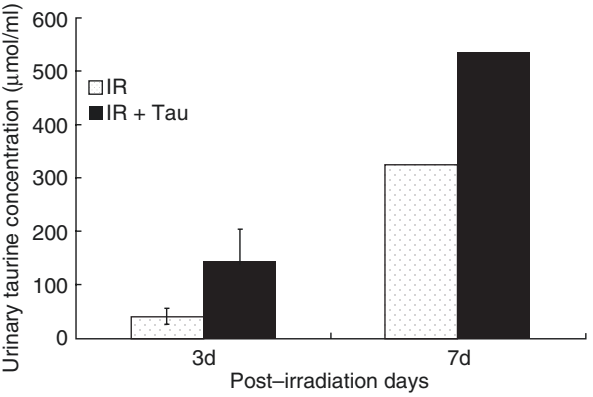

Fig. 3 The effects of the administration of taurine and irradiation on the urinary taurine concentration. Male ICR mice (n = 9) were exposed to whole body X-ray irradiation (7 Gy/mouse). Taurine (3000 mg/kg/day) taurine was given as part of the drinking water to rats in the starting at 30 min after irradiation. Data are shown as the mean ± SE. The urinary taurine concentration of IR + Tau group increased more than that of IR group

3.2 Localization of Taurine and Taurine Transporter After X-Irradiation in Mouse Small Intestine

The effect of radiation on the small intestine of mice is shown in Fig. 4. Ten days after irradiation, villus in the small intestine of IR group and IR + Tau group were shorter than that of a normal small intestine. The effect of radiation on the

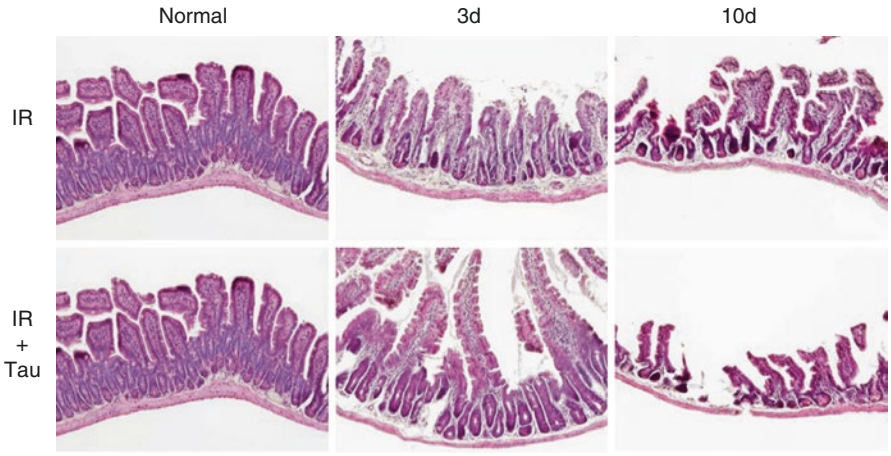

Fig. 4 Histological evidence of intestinal injuries—in mice after 7 Gy whole body X-irradiation. Representative intestinal sections stained with H&E are shown (200×). Taurine was given orally at 3000 mg/kg/day as part as part of the drinking water to rats in the IR + Tau group at 30 min after irradiation. Ten days after irradiation, the villi in the small intestine of IR group and IR + Tau group were found shorter than those in a normal small intestine

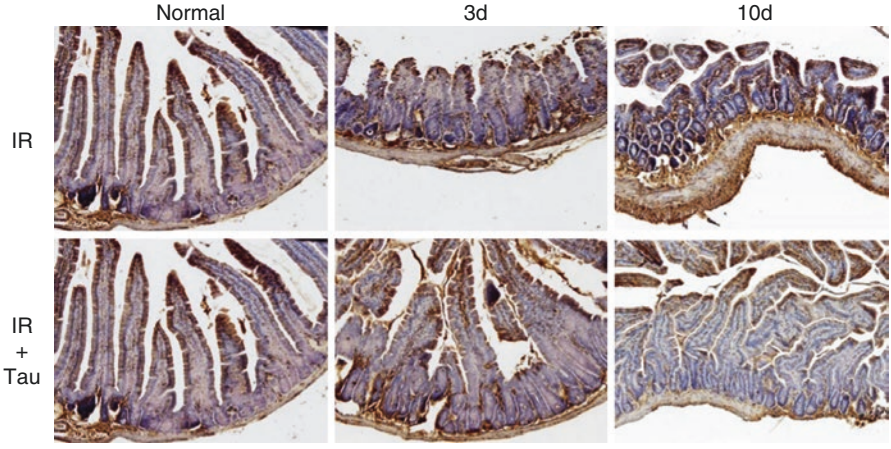

Fig. 5 Histological evidence of intestinal injuries in mice after 7 Gy whole body X-ray irradiation. Representative intestinal sections stained with H&E are shown (200×). Taurine, 3000 mg/kg/day was given orally as part of the drinking water to rats in the IR + Tau group. Taurine was administered at 30 min after irradiation. Three days and 10 days after X-ray irradiation, the expression of taurine in the small intestine of IR group and IR + Tau group decreased more than that of normal small intestine

expression of taurine/taurine transporter in the small intestine of mice is shown in Figs. 5 and 6. The expression of taurine/taurine transporter was reduced after radiation exposure.

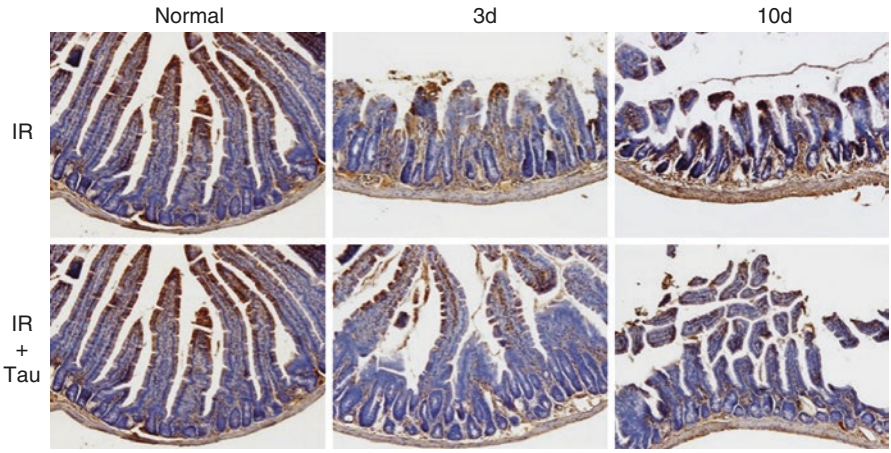

Fig. 6 Histological evidence of intestinal injuries in mice after 7 Gy whole body X-ray irradiation. Representative intestinal sections stained with H&E are shown (magnification 200×). Taurine, 3000 mg/kg/day was given as part of the drinking water to rays in the IR + Tau group. Taurine was administered 30 min after irradiation. Three days and 10 days after irradiation, the expression of taurine transporter in the small intestine of IR group and IR + Tau group decreased more than that of a normal small intestine

4 Discussion

Radiation exposure generates ROS and free radicals in irradiated cells. Excessive free radical generation is leading cause of oxidative stress. Physiological roles of taurine include an antioxidant action and protection of the body by inhibiting ROS and free radical formation (Johnson et al. 2012). The protective effect of taurine against organ damage caused by ischemia and reperfusion may be due to antioxidant action (Hanna et al. 2004). Ueno et al. (2007) has reported the functional recovery of rat administered of taurine after reperfusion Organ damage caused by ischemia/reperfusion and radiation exposure may be due to oxidative stress (Kingston et al. 2004; Asghari et al. 2016; Agrawal and Kale 2001). Therefore, the administration of taurine before or after irradiation might have a protective effect or aid in the recovery from organ damage.

Radiation can cause injury to hematopoietic and gastrointestinal systems depending on the dose of radiation received (Suman et al. 2012). Morphological changes of the intestinal mucosa after a high radiation exposure dose have been well documented (Driák et al. 2008; Labéjof et al. 2002), but molecular events that regulate intestinal epithelial cells radio-sensitivity and radiation-induced gastrointestinal injuries are not fully understood (Li et al. 2015). Abe et al. (1968) have reported an increase in the survival of mice to radiation exposure upon receiving taurine after the exposure although the effect was less than when administered before the exposure possibly because of a decrease in uptake after irradiation. Therefore, we examined the effect of taurine administration after a radiation exposure on the survival

rate, blood lymphocytes count and urinary taurine concentration in the whole body irradiation mouse model. This model is a well-established one that has been used to evaluate the radioprotective and radiation mitigation effect of chemical or of dietary compounds such as yeast-derived beta-glucan, melatonin and vitamin C against cellular damage (Gu et al. 2008; Rostami et al. 2016).

In the present study, taurine was not able to improve the survival rate after exposure to a high dose of radiation. This result is most likely due to incomplete recovery from an intestinal injury and to immune response deficiency. Therefore, to examine the role of taurine on the immune system and on the count of peripheral blood lymphocytes in mice after irradiation. In the present study, the administration of taurine led to an early recovery pf the lymphocytes count. Since taurine has been reported to function as a growth factor for lymphocytes or for lymphocyte progenitor cells (Fazzino et al. 2010), it is likely that this amino acid is promoting the growth factor for lymphocytes after exposure to a high dose of radiation.

Several studies have shown that the urinary excretion of taurine increases after irradiation (Goyer and Yin 1967; Johnson et al. 2012; Watson 1962). However, the precise cause for such an increase remains unknown. We also observed that a radiation exposure increased the urinary taurine concentration. Similarly, a high dose of radiation affects the gastrointestinal system. Radiation-induced gastrointestinal injury is primarily due to death of epithelial stem cells of the crypts (Ghosh et al. 2012). Finding that radiation increases the urinary elimination of taurine suggests that taurine might be release from the injury tissue. A taurine depletion will be harmful because it may inhibit the recovery of physiological functions depending on cellular growth, immune system and intestinal mucosa function.

Severe damage to the small intestine could the lead to malabsorption of taurine. It is reported that taurine uptake is associated with an increased expression of the taurine transporter (Warskulat et al. 2004). Therefore, to evaluate the mechanism of the radioprotective effect and radiation mitigation effect of taurine in the small intestine of mouse, we evaluated the expression of the taurine transporter. Histopathology is a well-established model that has been used to evaluate radioprotection and radiation mitigators against hematopoietic/gastrointestinal damage in mouse after irradiation (Zhang et al. 2003). Radiation exposure has been shown to induce apoptosis in cells (Singh et al. 2013). It is reported that taurine attenuates apoptosis (Maher et al. 2005). In the present study, radiation exposure inflicted severe damage to villi in the small intestine. This result suggests that taurine cannot attenuate apoptosis after a high dose of radiation. In fact, the expression of taurine/taurine transporter was reduced after radiation exposure. The intestinal injury after exposure to a high dose of radiation was associated with a decreased expression of the taurine transporter. Taurine uptake might be decreased in the small intestine after irradiation. These results indicate that exposure to a high dose of radiation induces cell damage and that taurine is unable to mediate recovery or repair against these changes. Thus, although taurine can mobilize hematopoietic cells to protect against the cellular damage by a high dose of radiation it, however, cannot aid in recover from intestinal injuries when given after a radiation exposure. It is also known that taurine losses have occurred after irradiation (Bezkrovnaia and Kostesha

1990). Therefore, taurine administration after irradiation might be beneficial to compensate for the taurine losses. In any event, a future study will be necessary to examine the effect of taurine after exposure to a low dose of radiation.

Taurine transporter, oxidative stress and inflammatory response-associated mechanisms are involved in radiation-induced gastrointestinal injury. We found that exposure to a high dose of radiation decreases the expression of the taurine transporter in the small intestine of the mouse. It is conceivable that the recovery/repair of radiation injury caused by taurine administration, as used in the present study, is not sufficiently pronounced to have a beneficial effect on intestinal injury after high dose of radiation exposure. Hence, the change of taurine transporter expression in response to different doses of radiation needs to be further investigated. These findings have significant implications to radiation exposure of civilians in nuclear plant accidents such as the one that took place in Fukushima, Japan.

5 Conclusion

In summary, a high dose of radiation exposure is found to decrease the expression of taurine transporter in the small intestine of mouse. Taurine may not necessarily be a good protectant when administered after high dose of radiation exposure but it might have a mitigating effect after low dose radiation exposure. The results of this study also indicate that by using a low dose of radiation it might be possible to explain the relationship between the mitigating mechanism of taurine on the radiation exposure and the expression of the intestinal taurine transporter.

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