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Potential inhibitory effects of low-dose thoron inhalation and ascorbic acid administration on alcohol-induced hepatopathy in mice

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ABSTRACT

Although thoron inhalation exerts antioxidative effects in several organs, there are no reports on whether it inhibits oxidative stress-induced damage. In this study, we examined the combined effects of thoron inhalation and ascorbic acid (AA) administration on alcohol-induced liver damage. Mice were subjected to thoron inhalation at 500 or 2000 Bq/m^3 and were administered 50% ethanol (alcohol) and 300 mg/kg AA. Results showed that although alcohol administration increased the levels of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in the serum, the combination of thoron inhalation (500 Bq/m^3) and AA administration 24 h after alcohol administration effectively inhibited alcohol-induced liver damage. The combination of thoron inhalation (500 Bq/m^3) and AA administration 24 h after alcohol administration increased catalase (CAT) activity. Alcohol administration significantly decreased glutathione (GSH) levels in the liver. The GSH content in the liver after 2000 Bq/m^3 thoron inhalation was lower than that after 500 Bq/m^3 thoron inhalation. These findings suggest that the combination of thoron inhalation at 500 Bq/m^3 and AA administration has positive effects on the recovery from alcohol-induced liver damage. The results also suggested that thoron inhalation at 500 Bq/m^3 was more effective than that at 2000 Bq/m^3, possibly because of the decrease in GSH content in the liver. In conclusion, the combination of thoron inhalation at 500 Bq/m^3 and AA administration promoted an early recovery from alcohol-induced liver damage.

Keywords: alcohol-induced liver damage; oxidative stress; antioxidative function; ascorbic acid (AA); thoron

INTRODUCTION

Radon (^{222}Rn) inhalation activates antioxidative functions and inhibits oxidative stress-induced damage in mice [1]. For example, radon inhalation inhibits alcohol-induced acute hepatopathy [2], which is induced by free radicals or reactive oxygen species (ROS).

Treatment of some pain-related diseases, such as rheumatoid arthritis [3, 4], may involve radon therapy, where inhalation treatment using radon gas is applied [5]. There are two types of radon sources: hot springs [6] and galleries [7, 8]. However, the application of radon therapy is limited owing to the scarcity of natural radon sources. Therefore, thoron (^{220}Rn; Tn), a radioisotope of radon, may be useful for reproducing an artificial radon treatment environment. Interestingly, we previously reported that thoron inhalation also has antioxidative effects [9]. Our findings suggested that thoron inhalation could be used for the treatment of ROS-related diseases.

The bioactive characteristics of thoron differ from those of radon. One of the probable reasons for this is the difference in physical characteristics. For example, the half-life of radon is 3.8 days, whereas

that of thoron is 55.6 seconds. These differences may affect the distribution of radon or thoron in the body. Another difference is in the α-particle energy emitted; the α-particle energy emitted by radon is 5.490 MeV, whereas that emitted by thoron is 6.288 MeV. In addition, the radioactive characteristics of radon progenies differ from those of thoron progenies. Moreover, the dose conversion factors of radon and thoron progenies are 16.8 and 107 nSv $(\mathrm{Bq\,m^{-3}\,h})^{-1}$, respectively [10]. Thus, their biological effects are different.

Previously, we reported that artificial thoron hot springs show beneficial effects for human health [11]. To enhance the health effects and reduce the exposure dose, a combination of thoron inhalation and antioxidant treatment may be useful, based on our previous findings [12]. Ascorbic acid (AA), or vitamin C, may be one of choices, as it is abundant in some foods, including lemons.

Several attempts have been made to reproduce radon therapy conditions using monazite [9], which contains relatively high levels of thorium. Thus, according to the availability of monazite, it may be used for practical medical applications without depending on natural radon sources. Our previous animal study using materials including a small amount of thorium series showed that thoron concentration in the air was sufficient to activate antioxidative functions in mice [9]. However, there are no reports of thoron inhalation inhibiting oxidative stress-induced damage. Based on our previous research, hepatopathy may be a possible indication for radon therapy [1]. Moreover, another study reported that thoron has a stronger physiological effect than radon [9]. Therefore, to further investigate and confirm the underlying mechanisms in mice, we adopted an alcohol administration method that can easily induce hepatopathy.

In this study, we aimed to examine whether thoron inhalation inhibits oxidative stress-induced damage. We used a mouse model of alcohol-induced oxidative damage for the following reasons: antioxidative effects induced by radon inhalation in the liver have already been reported [2]; effects of radon on alcohol-induced hepatopathy in terms of alleviating oxidative stress have also been reported [13]. Thoron concentrations were determined based on our previous study [9]. Despite the lack of epidemiological evidence for the cancer risk induced by thoron inhalation [10], we used low thoron doses in combination with AA, which is a widely used antioxidant.

MATERIALS AND METHODS

Animals

Male C57BL/6 N mice (8 weeks old) were purchased from CLEA Japan (Tokyo, Japan). This experimental protocol was approved by the Animal Care and Use Committee of Okayama University. Mice were housed at room temperature ($22 \pm 2^{\circ}$C) during the experiment.

Experimental protocol

The mice were divided into 24 groups. There were 5–7 mice in each group. The details of the experimental conditions are shown in Fig. 1. The mice were exposed to thoron at 500, or 2000 Bq/m^3 for 24 h. Next, AA and alcohol or alcohol only were administered to the mice. After 6 h (Fig. 1A) or 24 h (Fig. 1B) of incubation, the mice were euthanized using CO_2.

The mice were first administered AA and then exposed to thoron at concentrations of 500, or 2000 Bq/m^3 for 24 h. Subsequently, the mice were administered alcohol. At 24 h after administration, the mice were euthanized with CO_2 (Fig. 1C).

Thoron inhalation

Mice were exposed to thoron at concentrations of 500, or 2000 Bq/m^3 for 1 d using our exposure system [9]. The sham inhalation group was exposed to ambient air using an exposure system. The coefficients of variance for thoron concentrations during the exposure were 10% or lower.

Alcohol and ascorbic acid administration

The mice were intraperitoneally administered AA (Kanto Chemica. Co. Inc. Tokyo, Japan) at a dose of 300 mg/kg body weight. Immediately after AA administration, the mice were intraperitoneally administered 50% ethanol at a concentration of 5.0 g/kg bodyweight. The concentration of AA administered was determined in our previous study [12]. The livers were removed quickly after euthanasia using CO_2. Blood was collected from the heart and serum was separated by centrifugation at 3000 $\times$ *g* for 5 min at 4°C. The supernatant and liver were preserved at −80°C until the assay.

Biochemical assays

The levels of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in the serum and the level of triglyceride (TG) in the liver were assayed using an assay kit (Wako Pure Chemical Industry, Co., Ltd., Osaka, Japan).

Superoxide dismutase (SOD), catalase (CAT), total glutathione (t-GSH) and total protein levels in the liver were assayed using assay kits (SOD: Dojindo molecular Technologies, Inc., Kumamoto, Japan; CAT: Cayman Chemical, MI, USA; t-GSH: OXIS Health Products, Inc., Portland, OR, USA; total protein: Dojindo Molecular Technologies, Inc., Kumamoto, Japan). They were measured following the method described previously [14, 15].

Statistical analyses

Each data point is a ratio of the activity or content compared with that of the control group. The data are presented as the mean ± standard error of the mean. Statistical significance of the differences was determined using Tukey's test for multiple comparisons, followed by a one-way analysis of variance. Data were considered statistically significant at $P < 0.05$.

RESULTS

Effects of thoron inhalation followed by AA administration on hepatic functions and TG accumulation in the liver at 6 h after alcohol administration

GOT activities in the serum of all groups and GPT activities of Sham + Alco (500–6, 2000–6), Tn + Alco (500–6, 2000–6) and Tn + AA + Alco (500–6, 2000–6) groups were significantly higher than those in the control group. GOT activity in the serum of the Tn + AA + Alco (2000–6) group was significantly higher than that in the serum of the Sham + AA + Alco (2000–6) group (Fig. 2A). The TG levels in the livers of the Sham + AA + Alco (2000–6) group were significantly higher than those in the livers of the control (2000–6) group (Fig. 2B).

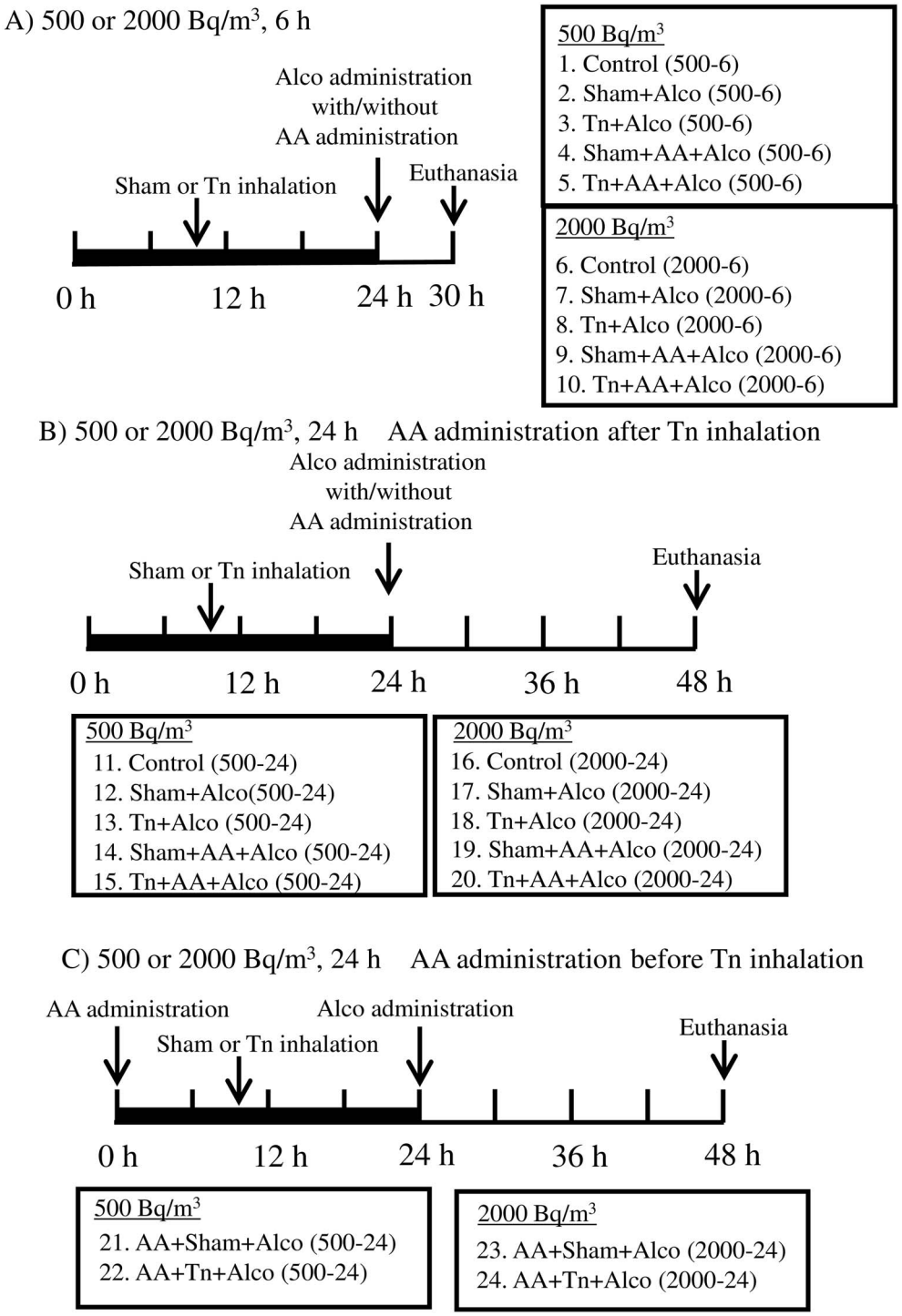

Fig. 1. Experimental procedure. Mice were treated with thoron (Tn), Alcohol (Alco), AA. (A) AA administration after Tn inhalation at a concentration of 500 or 2000 Bq/m³ for 6 h; (B) AA administration after Tn inhalation at a concentration of 500 or 2000 Bq/m³ for 24 h; (C) AA administration before Tn inhalation at a concentration of 500 or 2000 Bq/m³ for 24 h.

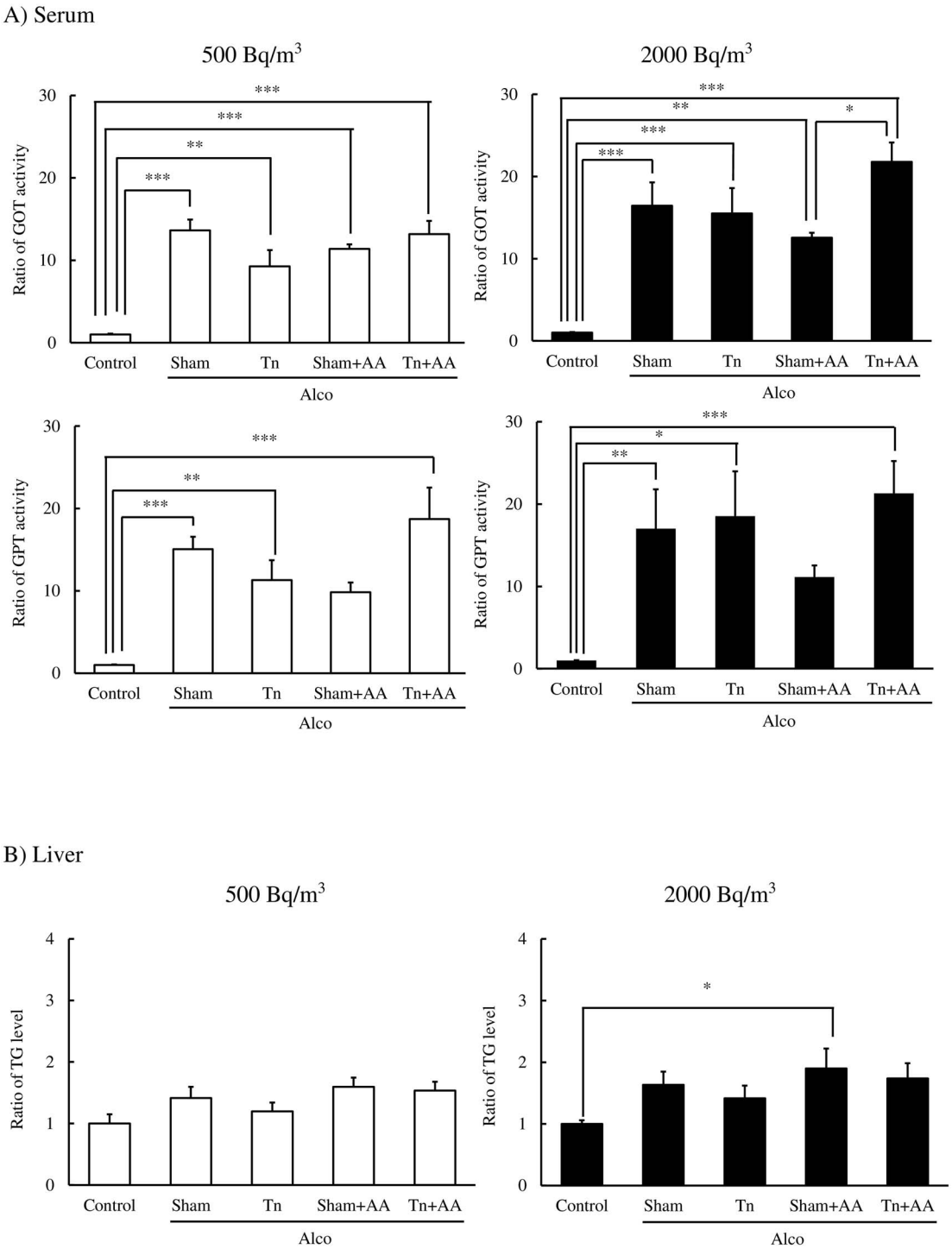

Fig. 2. Effects of thoron inhalation followed by AA administration on hepatic functions and TG accumulation in the liver at 6 h after alcohol administration (Fig. 1A). Mean ± standard error of mean (SEM), $n = 5–7$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

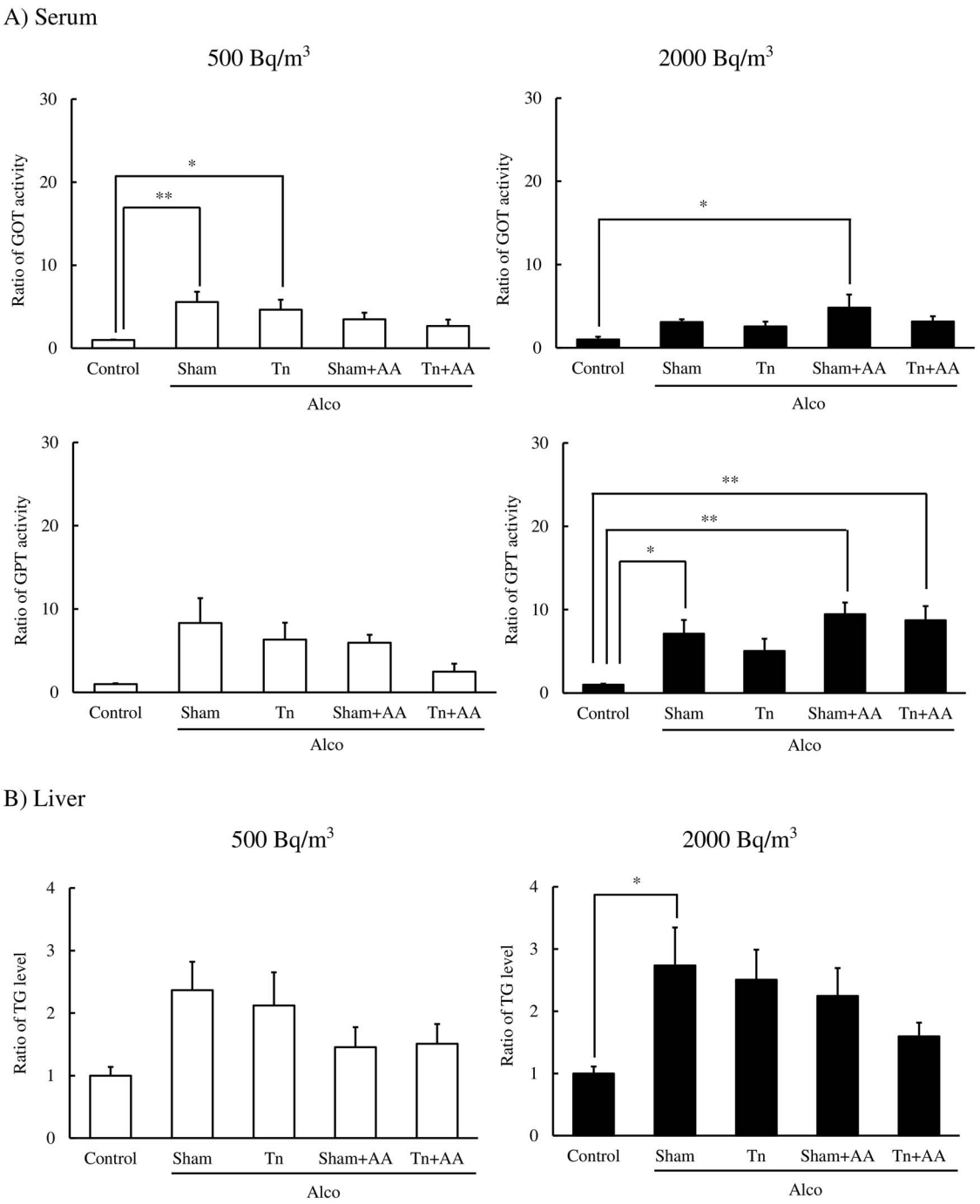

Fig. 3. Effects of thoron inhalation followed by AA administration on hepatic functions and TG accumulation in the liver at 24 h after alcohol administration (Fig. 1B). Mean ± standard error of mean (SEM), $n = 6–7$, $^{*}P < 0.05$, $^{**}P < 0.01$.

Effects of thoron inhalation followed by AA administration on hepatic functions and TG accumulation in the liver at 24 h after alcohol administration

GOT activities in the serum of Sham + Alco (500–24), Tn + Alco (500–24) and Sham + AA + Alco (2000–24) groups were significantly higher than those in the serum of the control group. GPT activities in the serum of Sham + Alco (2000–24), Sham + AA + Alco (2000–24) and Tn + AA + Alco (2000–24) groups were significantly higher than those in the serum of the control (2000–24) group (Fig. 3A).

The TG levels in the livers of the Sham + Alco (2000–24) group were significantly higher than those in the livers of the control (2000–24) group (Fig. 3B).

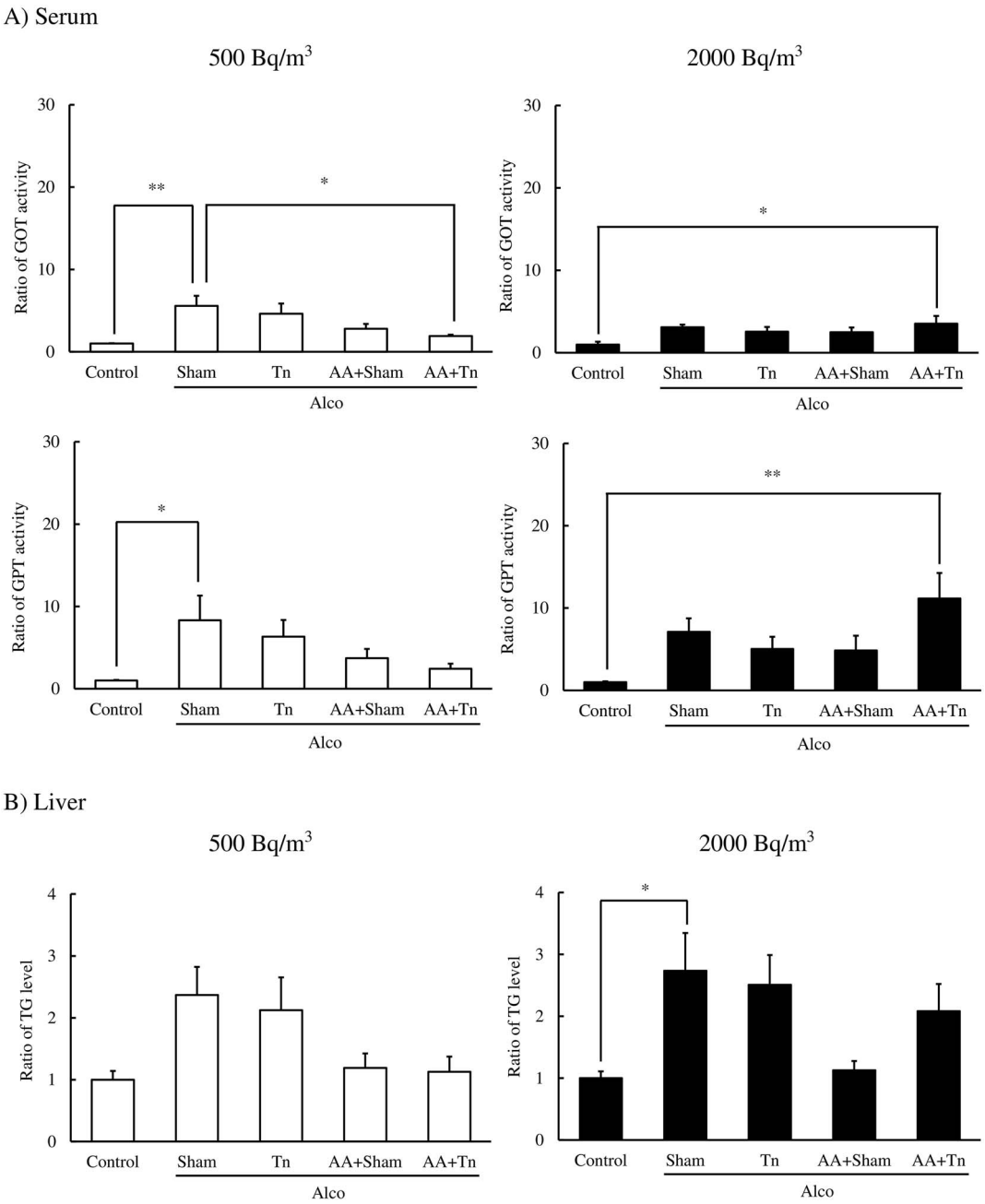

Fig. 4. Effects of thoron inhalation following AA administration on hepatic functions and TG accumulation in the liver at 24 h after alcohol administration (Fig. 1B Control, Sham + Alco, Tn + Alco, Fig. 1C). Mean ± standard error of mean (SEM), $n = 6–7$, $^{*}P < 0.05$, $^{**}P < 0.01$.

Effects of thoron inhalation following AA administration on hepatic functions and TG accumulation in the liver at 24 h after alcohol administration

The activities of GOT and GPT in the serum of Sham + Alco (500–24) and AA + Tn + Alco (2000–24) groups were significantly higher than those in the serum of the control group, while GOT activities in the serum of AA + Tn + Alco (500–24) group were significantly lower than those in the serum of the Sham + Alco (500–24) group (Fig. 4A).

Effects of thoron inhalation followed by AA administration on antioxidative functions in the liver at 6 h after alcohol administration

SOD activity in the liver of the Tn + AA + Alco (2000–6) group was significantly lower than that in the liver of the Sham + Alco (2000–6) and Sham + AA + Alco (2000–6) groups. CAT activity in the Tn + AA + Alco (500–6) group was significantly higher than that in the other groups. The t-GSH contents in the liver of Sham + Alco (500–6, 2000–6), Tn + Alco (500–6, 2000–6), Sham + AA + Alco

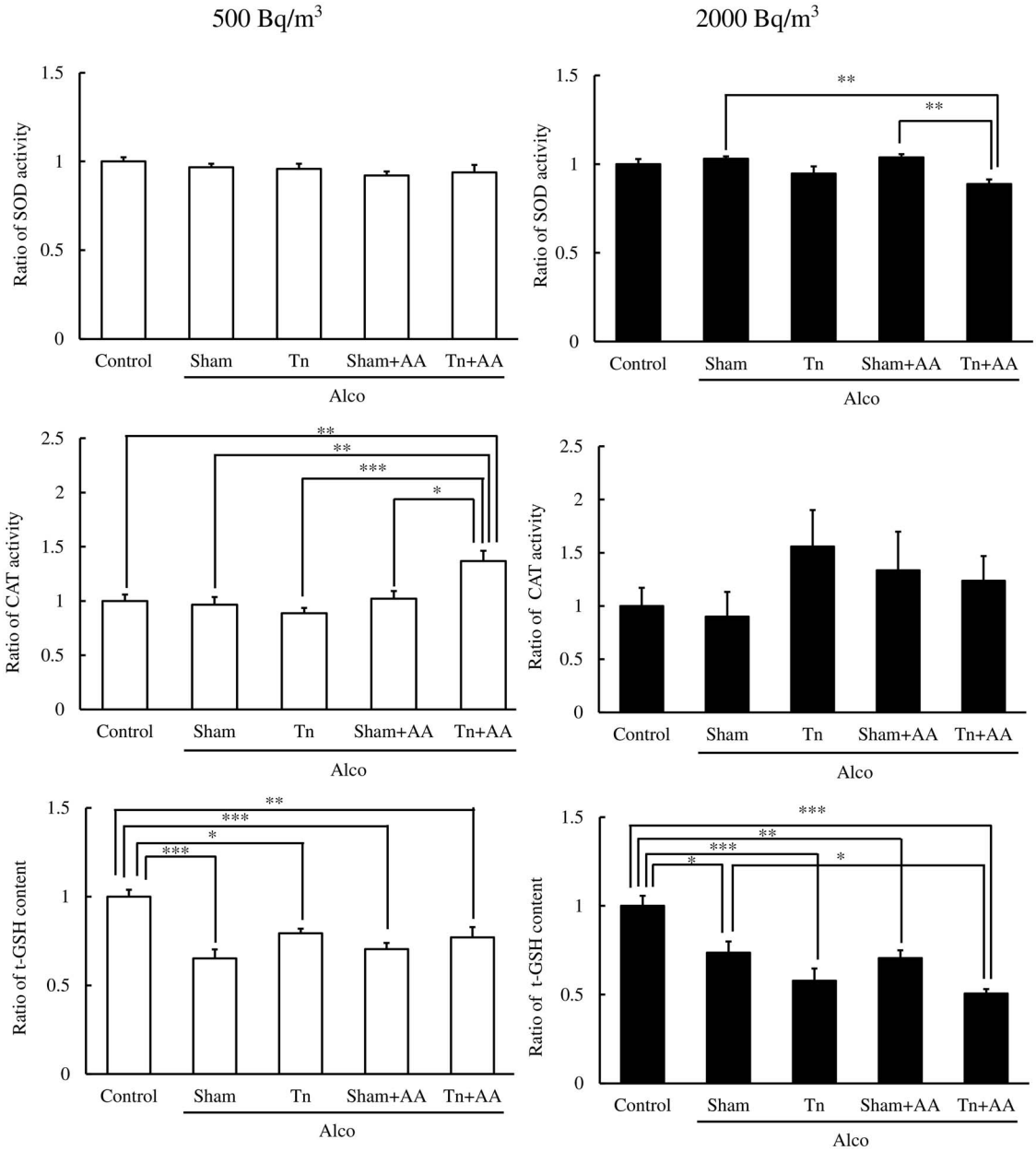

Fig. 5. Effects of thoron inhalation followed by AA administration on antioxidative functions in the liver at 6 h after alcohol administration (Fig. 1A). Mean ± standard error of mean (SEM), $n = 6–7$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

(500–6, 2000–6) and Tn + AA + Alco (500–6, 2000–6) groups were significantly lower than those in the control group. In addition, the t-GSH content in the liver of Tn + AA + Alco (2000–24) group was significantly lower than that in the liver of the Sham + Alco (2000–24) group (Fig. 5).

Effects of thoron inhalation followed by AA administration on antioxidative functions and TG accumulation in the liver at 24 h after alcohol administration

The t-GSH levels in the liver of Tn + Alco (2000–24), Sham + AA + Alco (2000–24) and Tn + AA + Alco (2000–24) groups were significantly lower than those in the liver of the control (2000–24) group. In addition, the t-GSH content in the liver of Tn + AA + Alco (2000–24) group was significantly lower than that in the liver of the Sham + Alco (2000–24) group (Fig. 6).

Effects of thoron inhalation following AA administration on antioxidative functions and TG accumulation in the liver at 24 h after alcohol administration

CAT activity in the liver of the AA + Sham + Alco (500–24) group was significantly lower than that in the liver of the control (500–24) and Sham + Alco (500–24) groups. The t-GSH content in the liver of

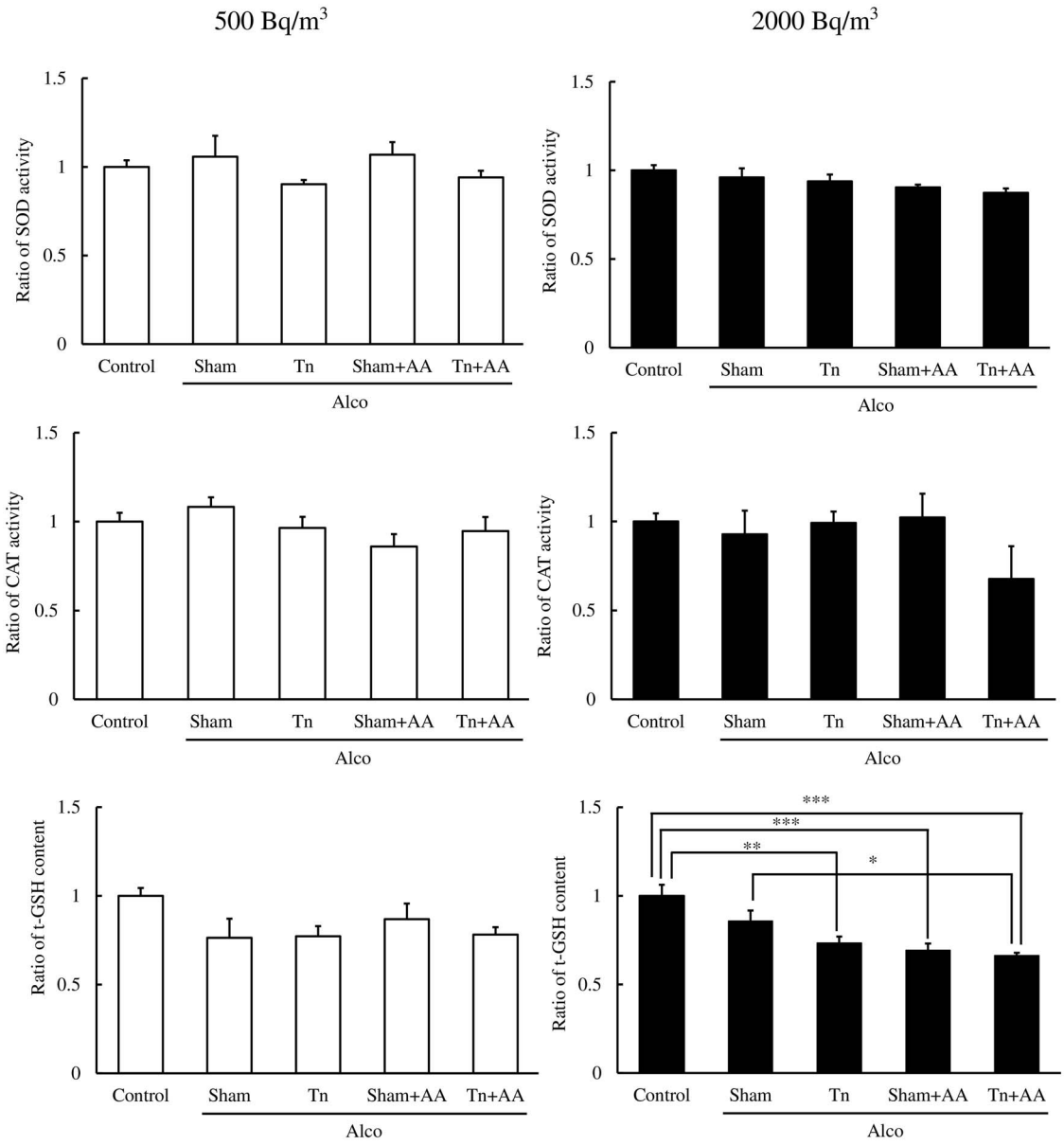

Fig. 6. Effects of thoron inhalation followed by AA administration on antioxidative functions in the liver at 24 h after alcohol administration (Fig. 1B). Mean ± standard error of mean (SEM), $n = 7$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

the Tn + Alco (2000–24) group was significantly lower than that in the liver of the control (2000–24) group (Fig. 7).

DISCUSSION

We reported that although thoron inhalation at 500 or 2000 Bq/m^3 for 24 h significantly increased t-GSH content in the normal mouse liver, lipid peroxidation (LPO) levels in the liver were significantly increased by thoron inhalation at 2000 Bq/m^3 [9]. This suggests that thoron inhalation at 2000 Bq/m^3 results in a redox imbalance in the liver. A high thoron concentration of approximately 530 kBq/m^3 decreased the activity of GSH peroxidase, an antioxidant enzyme, within 30 days of exposure, in the lung and heart and increased LPO levels [16]. We also reported that the combination of radon inhalation (2000 Bq/m^3) for 24 h and AA administration after radon inhalation effectively inhibited acute alcohol-induced liver damage [12]. In comparison, in the present study, we observed that the combination of thoron inhalation (500 Bq/m^3) and AA administration 24 h after alcohol administration effectively inhibited alcohol-induced liver damage (Figs 3 and 4). These results were similar to those of our previous study [12]. However, the combination of thoron inhalation (2000 Bq/m^3) and AA administration 24 h after alcohol administration did not inhibit alcohol-induced liver damage (Figs 3 and 4). The results showed a tendency similar to that in our previous study [9]. These findings

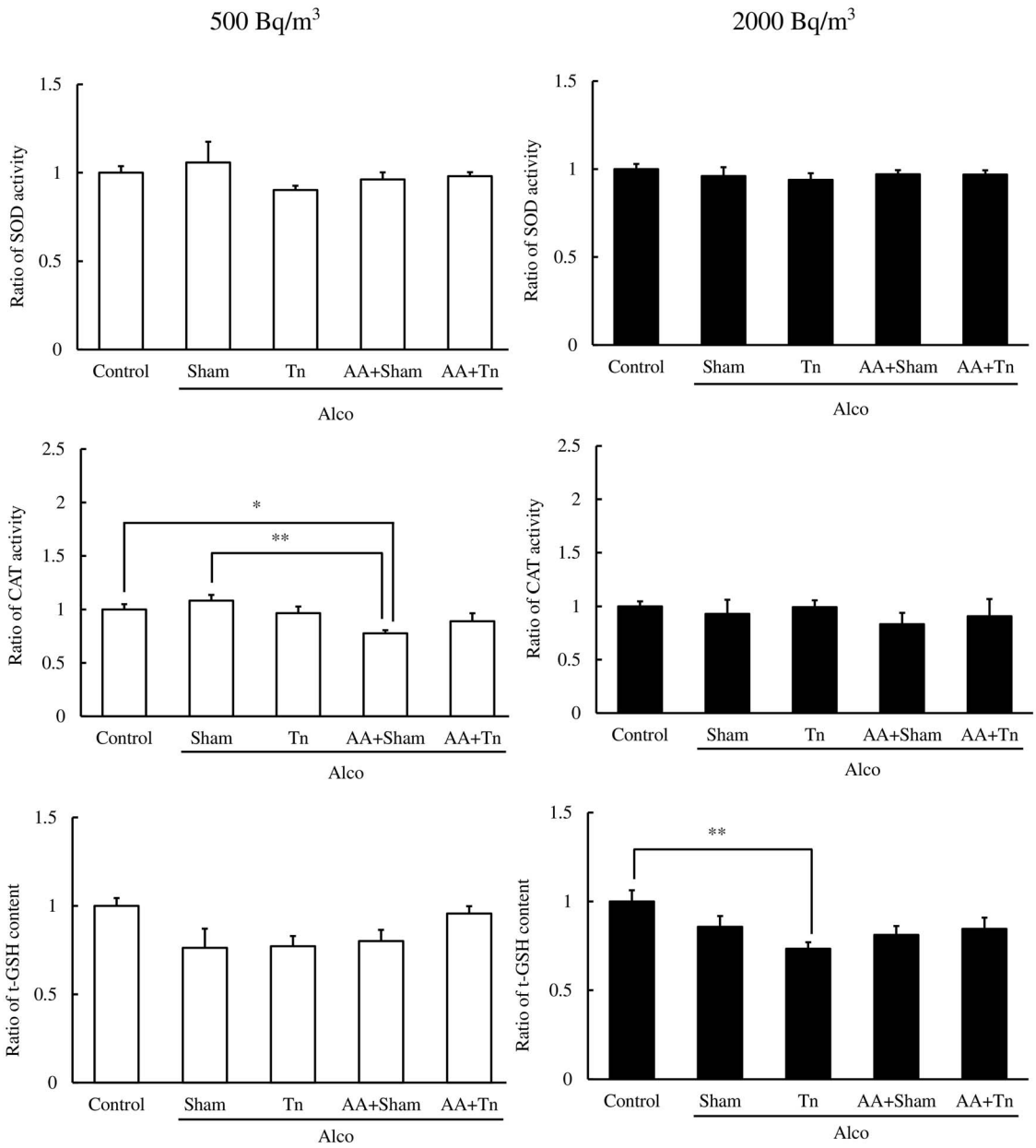

Fig. 7. Effects of thoron inhalation following AA administration on antioxidative functions in the liver at 24 h after alcohol administration (Fig. 1B Control, Sham + Alco, Tn + Alco, Fig. 1C). Mean ± standard error of mean (SEM), $n = 6–7$, $^{*}P < 0.05$, $^{**}P < 0.01$.

suggest that the optimal concentration for thoron inhalation with AA administration may be lower than that for radon inhalation.

AA is a widely used antioxidant. Non-enzymatic ascorbate reactions are involved in the detoxification of ROS, such as superoxide, hydroxyl, alkoxyl and peroxyl radicals [17]. This antioxidative property leads to the inhibition of hepatopathy induced by carbon tetrachloride [18], cypermethrin [19], organophosphate [20] and alcohol [21]. We also compared the effects of AA administration with pre-treatment or post-treatment of thoron inhalation on acute alcohol-induced liver damage because our previous study suggested that manganese SOD (Mn-SOD) activity is induced by moderate oxidative stress induced by radon [22] and inhibits alcohol-induced liver damage [23]. Therefore, pretreatment with AA may not induce antioxidative activities via thoron inhalation. Interestingly, the mitigation effects on alcohol-induced liver damage in the AA + Sham + Alco group seemed to be more effective than those in the Sham + AA + Alco group (Figs 3 and 4). It has been previously reported that the peak AA concentration in the liver after oral administration is approximately 3 hours, while the concentration is 25% of the peak at 24 hours [24]. Although the administration method was different from that used

in the present study, pre-treatment with AA may result in beneficial effects.

Ethanol is metabolized via three pathways which involve alcohol dehydrogenase, the microsomal ethanol oxidation system and CAT [25]. These pathways induce ROS production during ethanol metabolism. For example, GSH utilization increases whereas GSH synthesis decreases after a high-dose ethanol treatment [26]. Other reports have suggested that alcohol administration depletes GSH by inhibiting the expression of mitochondrial GSH transporter [27–29]. Thus, antioxidants play a critical role in the inhibition of alcohol-induced liver damage. An increase in the ratio of reduced GSH to oxidized GSH (GSSG) is an indicator of oxidative stress. On the other hand, intracellular GSH is usually present in the reduced form in most cases [30]. Therefore, in this study, we focused on t-GSH, which is the sum of the two. We previously reported that radon inhalation inhibits alcohol-induced liver damage [2] and that the combination of AA administration and radon inhalation exerts more beneficial effects against alcohol-induced liver damage [12]. In the present study, 6 h after alcohol administration, the GSH content in the liver significantly decreased (Fig. 5). In addition, GSH content in the livers of mice that inhaled thoron at 2000 Bq/m^3 with or without AA administration was lower than that in the livers of mice that inhaled thoron at 500 Bq/m^3 (Fig. 5). These results indicate differences in the inhibitory effects of thoron inhalation. Moreover, CAT activity in the liver of the Tn + AA + Alco (500–6) group was significantly higher than that in the livers of other groups (Fig. 5). CAT plays a role not only in the detoxification of ROS but also in alcohol metabolism, thereby resulting in the production of ROS [25]. This could also explain why the GPT activity in the Tn + AA+Alco (500–6) group increased. Another possible reason may be the state in which alcohol is not sufficiently digested naturally at 6 h after alcohol administration. As a result, both GOT and GPT activities increased. Figures 3 and 4 show that at 24 h spontaneous digestion had progressed after alcohol administration. By this time point, the inhalation of 500 Bq/m^3 Tn had promoted decreases in both GOT and GPT activity, as compared to the sham +Alco group. Moreover, the GSH content in the liver after AA administration before thoron inhalation at 2000 Bq/m^3 was closer to the control level than that after thoron inhalation (Figs 6 and 7). These findings suggest that pre-treatment with AA is more effective than post-treatment with AA.

In conclusion, the combination of thoron inhalation at 500 Bq/m^3 and AA administration resulted in the early recovery from alcohol-induced liver damage in mice. The results also suggest that thoron inhalation at 500 Bq/m^3 was more effective than that at 2000 Bq/m^3. Although the absorbed dose in the liver following radon inhalation was estimated in our previous study [31], we could not estimate the absorbed dose following thoron inhalation. In addition, since we did not examine concentration dependence, we cannot conclude whether or not these results depend on the concentration of AA. However, AA dose–response experiments may yield new insights. Furthermore, we also plan to conduct a more detailed study to include other indications and to determine the extent to which the dose of a therapeutic drug can be reduced if thoron inhalation is used as an add-on treatment. Estimation of the absorbed dose may provide clues to clarify the differences between radon and thoron inhalation.

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CONFLICT OF INTEREST

No conflicts of interest.

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