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Organ dependency in the enhancement of antioxidant functions by fractionated thermal and radon treatment

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Original Paper

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Organ dependency in the enhancement of antioxidant functions by fractionated thermal and radon treatment

Abstract

We previously reported that a combination of thermal treatment (TT) and radon inhalation may increase antioxidant activity in mouse organs. However, the effects are limited, and the conditions differ substantially from those of actual clinical radon balneotherapy. In this study, we evaluated the combined effects of TT and radon inhalation under a scheme that more closely resembled clinical settings. The treatments were administered three times a week (on Wednesdays, Fridays, and Mondays) over treatment durations of 1, 2, or 4 weeks. After each TT, radon was inhaled at a concentration of 2,000 Bq/m^3 for 24 h. The combination of TT and radon inhalation exerted a positive effect on antioxidant function in the spleen. The combined treatment also improved antioxidant function in the liver, pancreas, and colon; however, these effects diminished depending on treatment duration or antioxidant indices, indicating that the conditions for the interactions were limited. Conversely, the combination decreased antioxidant function in the brain, lungs, kidneys, and stomach and did not show interactive effects on antioxidant function in the heart and small intestine. These findings provide insight into the organ-specific effects of the combination of TT and radon inhalation.

Keywords: Thermal treatment; radon inhalation; fractionated treatment; antioxidant function

Introduction

Radon balneotherapy, using radon inhalation, has been used to treat various pain-related disorders in areas such as Misasa, Tottori Prefecture, Japan (Yamaoka et al. 2004; Mitsunobu et al. 2003). Similarly, in Bad Gastein, Austria, radon gallery therapy has been administered using former mining tunnels (Gaisberger et al. 2021). Both modalities involve a high-temperature and high-humidity environment, a maximum treatment duration of approximately 3–4 weeks, and a frequency of approximately 3 times per week for 40 min per session. In radon balneotherapy, multiple physiological stimuli, such as thermal stimulation and low-dose radiation stimulation from radon, are combined. The indications for radon therapy are primarily oxidative stress-related diseases; accordingly, we hypothesized that radon inhalation enhances antioxidant function. To evaluate the effects, we developed a radon exposure system for small animals (Ishimori et al. 2010; Kataoka et al. 2012). Using this system, we have demonstrated that radon inhalation increases total glutathione (t-GSH) content and glutathione peroxidase (GPx) activity in the liver and kidneys (Kataoka et al. 2011). This enhanced antioxidant function suggests a suppressive effect on carbon tetrachloride (CCl_4)-induced hepatic and renal damage (Kataoka et al. 2011). Furthermore, we have shown that levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), an indicator of oxidative DNA damage, decrease in certain organs following radon inhalation, indicating that oxidative stress-induced damage may be suppressed through the activation of antioxidant functions (Kataoka et al. 2021a). It has also been reported that nuclear factor-κB (NF-κB) activation is involved in manganese superoxide dismutase (Mn-SOD) induction in the mouse brain caused by radon inhalation, suggesting that radon stimulation influences antioxidant defense mechanisms via intracellular oxidative stress-response pathways (Kataoka et al. 2017).

Thermal stimulation affects antioxidant function and stress responses by

generating reactive oxygen species (ROS). Heat stress-induced ROS induces protective factors, such as heat shock protein 70 (HSP70) and Mn-SOD, via the p38 MAPK and Akt signaling pathways (Mustafi et al. 2009). Furthermore, mild heat stress at 40°C has been reported to induce antioxidant responses coupled with the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and ROS derived from mitochondria and NADPH oxidase (Hraoui et al. 2025). These findings indicate that thermal stimulation functions as a signal to induce adaptive cellular defense responses, partly through Nrf2, a feature shared by the antioxidant-enhancing effects of radon inhalation. However, little is known about the enhancement of antioxidant function through the combined use of radon inhalation and thermal treatment (TT). Distinct organ-specific antioxidant responses have been observed, such as increases in antioxidant function in the brain and large intestine, increases and decreases in the kidneys, and decreases in the lungs; however, validation of these combined treatment effects remains insufficient (Miyanaga et al. 2026). Furthermore, the conditions for TT and radon inhalation in previous studies differed substantially from those of actual clinical radon balneotherapy. Determining an effective combination of TT and radon inhalation would be valuable for exploring novel indications for radon therapy and for elucidating the mechanisms underlying symptom relief in established indications.

In this study, antioxidant functions were evaluated across various organs after fractionated combined exposure to TT and radon inhalation under a scheme that closely mirrors clinical settings.

Materials and methods

Animals

Male 8-week-old BALB/cJ mice purchased from Jackson Laboratory Japan, Inc.

(Yokohama, Japan) were used. The animals were kept under regulated environmental conditions on a 12-h light/dark cycle (08:00 to 20:00) and given ad libitum access to water and standard chow. The experiments were conducted using six mice per group (n = 6 per group across 12 groups, totaling 72 mice). All animal handling protocols were reviewed and approved by the Animal Care and Use Committee of Okayama University (approval no. OKU-2025540).

Thermal treatment

The TT and mock control conditions (non-TT) were applied using a commercial incubator (EI-300V; AS ONE Co., Ltd., Osaka, Japan). Prior to each session, the chamber was pre-warmed to 38.5°C for 30 min. The treatments were administered three times a week (on Wednesdays, Fridays, and Mondays) over treatment durations of 1, 2, or 4 weeks. To minimize fluctuations in chamber temperature during the TT, empty cages were preheated before the mice were placed in them. In the TT protocol, when the internal chamber temperature reached 39.0°C, the heating element was turned off until thermal conditions stabilized, after which heating was restarted. The non-TT control animals were maintained in an unpowered incubator. To observe signs of animal distress throughout the procedure, the opaque outer door was left open, and only the clear inner door was closed. The chamber temperatures were logged at 1-min intervals. Rectal temperatures were recorded before and immediately after each treatment using a digital thermometer (TK-60; Rixen, New Taipei City, Taiwan) to determine the average magnitude and percentage variation in core body temperature across the intervention period.

Radon inhalation

Radon inhalation therapy was initiated immediately after each TT session. The

sham group received sham inhalation for 24 h, whereas the radon inhalation group inhaled radon at an average concentration of approximately 2,000 Bq/m^3 in their cages for 24 h. Immediately following the completion of all treatments, the mice were euthanized by carbon dioxide inhalation. Subsequently, target organs (brain, lungs, heart, liver, stomach, spleen, pancreas, kidneys, small intestine, and colon) were harvested and stored at −80°C until further analyses.

Biochemical assays

Antioxidant function was evaluated as described previously (Miyanaga et al. 2026). Briefly, each tissue sample was homogenized in 10 mM phosphate-buffered saline (PBS) and centrifuged under the same conditions reported previously (Miyanaga et al. 2026). The resulting supernatant was diluted to an appropriate concentration. Superoxide dismutase (SOD) (SOD Assay Kit; WST Dojindo, Kumamoto, Japan), catalase (CAT) (Catalase Assay Kit; Cayman Chemical, USA), and t-GSH levels (BIOXYTECH GSH-420 Assay Kit; Oxis International, Inc., Tampa, FL, USA) were measured using commercial assay kits, following the manufacturers' instructions.

Statistical analysis

Antioxidant function data are expressed as the mean ± standard error of the mean. Group differences and interactions were evaluated using two-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test using JMP software. Statistical significance was set at $P<0.05$.

Results

Changes in rectal temperature and rate of variation induced by TT

The effects of the combination of TT and radon inhalation were evaluated based on comparisons with the Sham group.

TT elevated both rectal temperature and its rate of change significantly at 1, 2, and 4 weeks, irrespective of radon exposure, over those in the Sham group (Fig. 1).

Combination effects of TT and radon inhalation on antioxidant functions in spleen

In the spleen, a significant increase was observed exclusively in SOD activity following 2 weeks of combined intervention relative to that in the non-TT + Sham inhalation control (Fig. 2).

Combination effects of TT and radon inhalation on antioxidant functions in liver, pancreas, and colon

In the liver, 1 week of combined intervention produced a significant elevation in t-GSH content compared with that in the non-TT + Sham control; however, 2 weeks of combination therapy led to significant reductions in both SOD activity and the t-GSH content, followed by a significant increase in CAT activity at 4 weeks compared with those in the control group (Fig. 3).

In the pancreas, 2 weeks of combined treatment significantly boosted SOD activity, whereas CAT activity significantly decreased relative to those in the non-TT + Sham inhalation control (Fig. 4).

In the colon, 2 weeks of combined TT and radon inhalation resulted in significant increases in both SOD activity and t-GSH content, whereas 4 weeks of combined treatment significantly suppressed CAT activity compared with levels in the non-TT +

Sham group (Fig. 5).

Combination effects of TT and radon inhalation on antioxidant functions in brain, lung, kidney, and stomach

In the brain, 1 week of combined TT and radon inhalation produced a significant decline in CAT activity, whereas 2 and 4 weeks of combined treatment resulted in significant reductions in SOD activity relative to levels in the non-TT + Sham inhalation control (Fig. 6).

In the lungs, the combination therapy led to a significant decrease in CAT activity at 2 weeks and a significant suppression of SOD activity at 4 weeks compared with levels in the non-TT + Sham group (Fig. 7).

In the kidneys, CAT activity after 1 week of combined treatment and SOD activity after 2 weeks of combined treatment both exhibited significant decreases compared with levels in the non-TT + Sham inhalation group (Fig. 8).

In the stomach, 2 weeks of combined intervention caused a significant reduction in CAT activity (Fig. 9).

Combination effects of TT and radon inhalation on antioxidant functions in heart and small intestine

Regarding the heart and small intestine, combined intervention produced no statistically significant interactive alterations in any of the evaluated antioxidant parameters (Figs. 10 and 11).

Discussion

This study investigated how repeated combined TT and radon inhalation modulate the

antioxidant capacity in multiple murine tissues. Oxidative stress plays a major role in various diseases targeted by radon therapy. In this study, distinct organ-dependent outcomes emerged; antioxidant activity increased in the spleen but decreased in the brain, lungs, kidneys, and stomach. Effects in the liver, pancreas, and colon depended on the evaluated markers and exposure periods, whereas the heart and small intestine exhibited no marked alterations. Overall, our results indicate that the systemic effect of repeated combination therapy is heterogeneous and differs according to specific tissue types and physiological parameters.

Prior research has revealed organ-specific patterns in radon-induced antioxidant upregulation, with potential variations in baseline tissue redox status as an underlying factor (Kataoka et al. 2021b). Although organ-dependent variation in antioxidant enhancement was identified in our study, the observed trends diverged from earlier findings because more TT and radon sessions were applied. When mice were subjected to TT for 5 consecutive days, elevated baseline expression of HSP72 and HSP90 in the lungs, heart, spleen, liver, and brain as well as a blunting of the magnitude of increase in HSP72 expression were observed (Sareh et al. 2011). This phenomenon is known as heat acclimation (McClung et al. 2008), and although basal oxidative stress levels are elevated, it has been reported to confer protective effects against changes in oxidative stress induced by acute exhaustive exercise in hot environments (Kaldur et al. 2014). Studies in humans have also shown that once- and twice-daily heat acclimation confer similar magnitudes of heat adaptation and exercise tolerance improvements without differentially altering immune function (Willmott et al. 2018). Therefore, the difference in the effects of TT between our previous studies and the present experimental conditions may be attributed mainly to the number of TTs (total stimulus dose) rather than to the treatment method (e.g., continuous or intermittent) itself.

A previous study has reported that heat stress increases SOD activity in the liver and elevates lipid peroxidation levels in the kidney (Jacobs et al. 2020). The present study provides the first evidence, to the best of our knowledge, that SOD activity in the spleen increases in response to the combined treatment. Furthermore, in our previous study, the enhancement of antioxidant function was not observed after a combination of TT and radon inhalation (Miyanaga et al. 2026). Given that an increase in SOD activity is induced by moderate oxidative stress (Mustafi et al. 2009), the present conditions may effectively enhance antioxidant function in the spleen.

Excessive oxidative stress compromises antioxidant defense. For example, in rats, exposure to radon at 3,000 kBq/m^3 for 3 h elevated SOD activity in the liver, kidneys, and spleen, whereas prolonged exposure to 1,600 kBq/m^3 for 16 h significantly attenuated SOD activity (Ma et al. 1996). In our study, the antioxidant capacity in the colon increased transiently at 2 weeks but declined by 4 weeks, implying that 4 weeks of co-treatment with hyperthermia and radon exposure inflicted a suprathreshold oxidative load on the colon. Conversely, the liver exhibited dynamic fluctuations, with elevated antioxidant defenses at 1 and 4 weeks, interrupted by a decline at 2 weeks. Such nonlinear temporal variations align with the characteristic responses observed in low-dose X-ray-induced antioxidant hormesis (Yamaoka et al. 1991). Taken together, these findings suggest that oxidative stress-mediated pathologies could be mitigated by a 2-week intervention in the colon, whereas a 1- or 4-week regimen may be optimal for the liver.

A previous series of studies also demonstrated that the timing of enhanced antioxidant function and its response characteristics following low-dose radiation exposure varied depending on the evaluation parameter. A typical example is the change in SOD activity over time after X-ray irradiation (Yamaoka et al. 1991). That is, biochemical data obtained from sample collection at a single time point do not necessarily reflect the overall redox

(reduction-oxidation) state integrated over the preceding period. Therefore, based solely on the findings in the pancreas in this study, where SOD activity increased while CAT activity decreased after 2 weeks of combined treatment, objectively determining whether the total antioxidant function was truly enhanced is difficult. To clarify these comprehensive changes, it would be useful to establish a disease model in which oxidative stress is induced in the pancreas and evaluate the suppressive effect of this treatment on pathogenesis. If oxidative stress-induced disease is successfully suppressed, it can be concluded that overall antioxidant function is enhanced. However, the protocol of this experiment alone was insufficient to definitively determine the presence or absence of the combined effects on the pancreas.

In previous work demonstrating the reduction in antioxidant capacity following combined TT and radon inhalation, the effect was confined to the lungs (Miyanaga et al. 2026). In this study, decreased antioxidant function was observed in the brain, lungs, stomach, and kidneys. Collectively, these results suggest that the lungs are most vulnerable to the synergistic effects of hyperthermia and radon exposure. Radon is a well-established risk factor for pulmonary carcinogenesis (Maier et al. 2020; Al-Zoughool and Krewski 2009; Pershagen et al. 1994; World Health Organization 2009) and exerts a direct effect on the lung tissue during inhalation. Additionally, whereas previous findings indicated an upregulation of brain antioxidant defense mechanisms under the combined treatment, our results demonstrated a distinct downregulation. Given that the brain inherently maintains lower baseline antioxidant defenses (Kataoka et al. 2021b), relative to organs such as the liver or kidneys, its threshold for permissible oxidative stress is inherently narrow. Thus, the present experimental paradigm may have imposed a suprathreshold burden. Similarly, the kidneys and stomach, which previously exhibited inconsistent responses (fluctuating or remaining unchanged, respectively), demonstrated

a consistent functional decline in this study. Taken together, these observations suggest that the specific conditions employed in this study elicited excessive oxidative stress exceeding the physiological tolerance limits of these organs.

This study has a few limitations that warrant mention. First, simultaneous administration of TT and radon inhalation was technically infeasible, precluding the precise simulation of clinical balneotherapy conditions. While elevating the radon concentration within the incubator is possible, opening the door to transfer mice induces a substantial loss of radon, making it challenging to maintain target radon levels during a brief 40-min heating session. Second, HSPs were not evaluated in this experiment, as our primary focus was to evaluate antioxidant parameters relevant to oxidative stress-related disorders. To overcome these experimental constraints, a novel radon-exposure chamber for in vitro studies is under development, which will help elucidate the combined mechanism underlying the effects of thermal and radon therapies at the cellular level. Finally, although an upregulated antioxidant capacity was observed, we did not directly examine outcomes in specific pathological models; this aspect will be addressed in subsequent investigations.

In conclusion, our results suggest that the combination of TT and radon inhalation enhances antioxidant function in the spleen. Furthermore, although the enhancement of antioxidant function was observed in the liver, pancreas, and colon, these effects diminished depending on treatment duration or antioxidant indices, indicating that the conditions for these interactions were limited. In contrast, the combined treatment decreased antioxidant function in the brain, lungs, kidneys, and stomach, whereas no interactive effects were found in the heart and small intestine.

Author contributions

Conceptualization: T. K.; Investigation: M. N., A. T., S. M., R. T., S. G., K. T., and T. K. writing—original draft preparation: M. N. and T. K.; writing—review and editing: A. S., S. N., N. K., R. T., and K. Y.; supervision: T. K.; project administration: T. K.; funding acquisition: K. Y. and A. S. All authors have read and agreed to the published version of this manuscript.

Institutional review board statement

Approval number for this study: OKU-2025540.

Conflicts of interest

The authors declare no conflict of interest.

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Figure and table legends

Fig. 1 Changes in rectal temperature and its rate of variation induced by thermal treatment (TT). Mean ± SEM, n = 6, *P<0.05, **P<0.01, ***P<0.001 vs. non-TT + Sham, ###P<0.001 vs. non-TT + radon (Rn)

Fig. 2 Combination effects of TT and radon inhalation on antioxidant functions in spleen. Mean ± SEM, n = 6, *P<0.05, **P<0.01 vs. non-TT + Sham, ##P<0.01, ###P<0.001 vs. non-TT + radon (Rn), +++P<0.001 vs. TT + Sham

Fig. 3 Combination effects of TT and radon inhalation on antioxidant functions in liver. Mean ± SEM, n = 6, *P<0.05, **P<0.01 vs. non-TT + Sham, #P<0.05, ##P<0.01, ###P<0.001 vs. non-TT + radon (Rn)

Fig. 4 Combination effects of TT and radon inhalation on antioxidant functions in pancreas. Mean ± SEM, n = 6, *P<0.05, ***P<0.001, vs. non-TT + Sham, #P<0.05, ###P<0.001 vs. non-TT + radon (Rn), +++P<0.001 vs. TT + Sham

Fig. 5 Combination effects of TT and radon inhalation on antioxidant functions in colon. Mean ± SEM, n = 6, *P<0.05, ***P<0.001, vs. non-TT + Sham, ##P<0.01, ###P<0.001 vs. non-TT + radon (Rn), ++P<0.01 vs. TT + Sham

Fig. 6 Combination effects of TT and radon inhalation on antioxidant functions in brain. Mean ± SEM, n = 6, *P<0.05 vs. non-TT + Sham, ##P<0.01 vs. non-TT + radon (Rn), +++P<0.001 vs. TT + Sham

Fig. 7 Combination effects of TT and radon inhalation on antioxidant functions in lung. Mean ± SEM, n = 6, *P<0.05, **P<0.01, ***P<0.001, vs. non-TT + Sham, $^{\#}$P<0.05, $^{\#\#\#}$P<0.001 vs. non-TT + radon (Rn)

Fig. 8 Combination effects of TT and radon inhalation on antioxidant functions in kidney. Mean ± SEM, n = 6, *P<0.05 vs. non-TT + Sham, $^{\#\#}$P<0.01 vs. non-TT + radon (Rn)

Fig. 9 Combination effects of TT and radon inhalation on antioxidant functions in stomach. Mean ± SEM, n = 6, *P<0.05, **P<0.01 vs. non-TT + Sham

Fig. 10 Combination effects of TT and radon inhalation on antioxidant functions in heart. Mean ± SEM, n = 6, *P<0.05 vs. non-TT + Sham, $^{\#}$P<0.05, $^{\#\#}$P<0.01 vs. non-TT + radon (Rn)

Fig. 11 Combination effects of TT and radon inhalation on antioxidant functions in small intestine. Mean ± SEM, n = 6, *P<0.05 vs. non-TT + Sham, $^{\#\#}$P<0.01 vs. non-TT + radon (Rn)

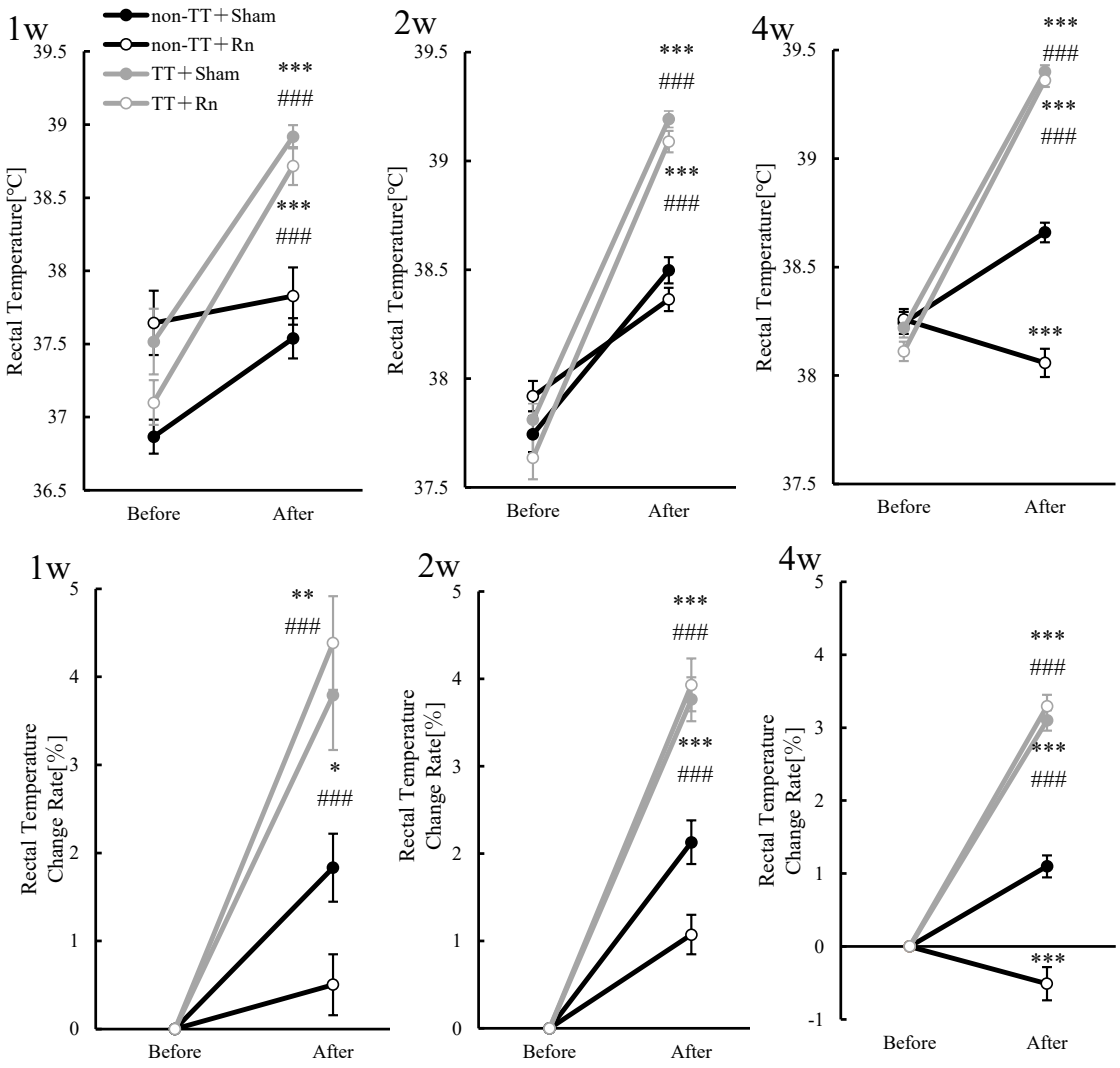


Fig.1 Changes in Rectal Temperature and that rate

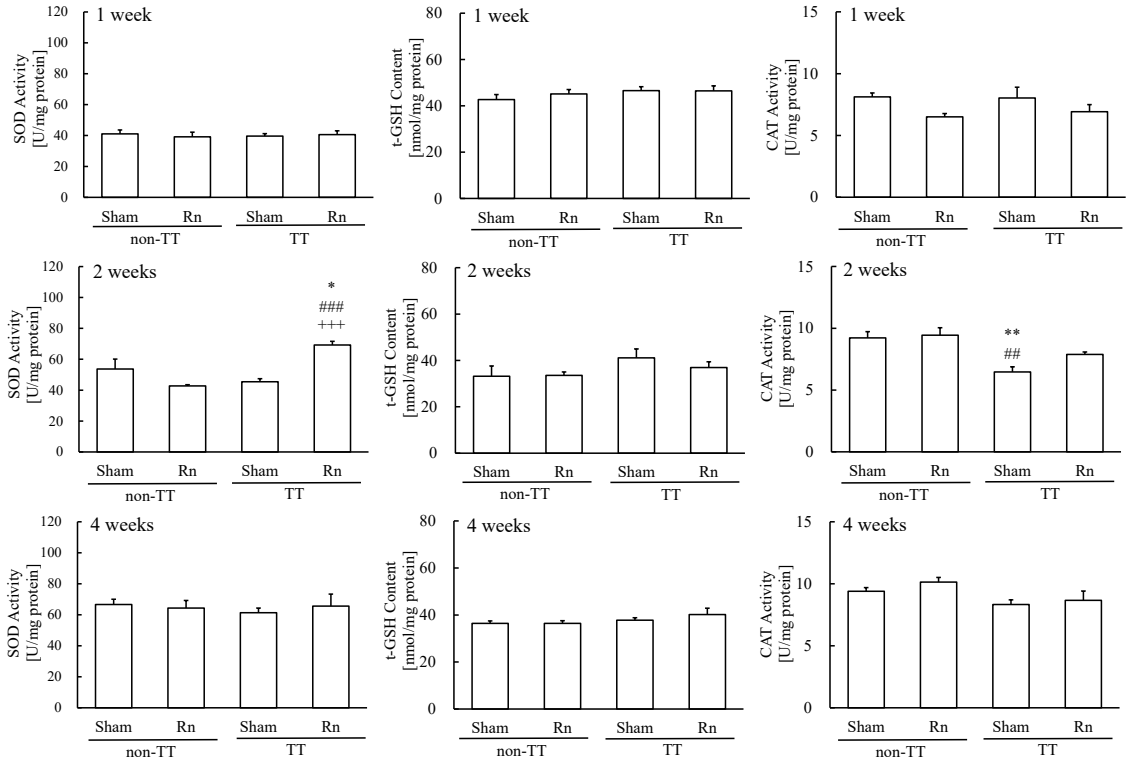

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT
*
###
+++
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Fig.2 Spleen

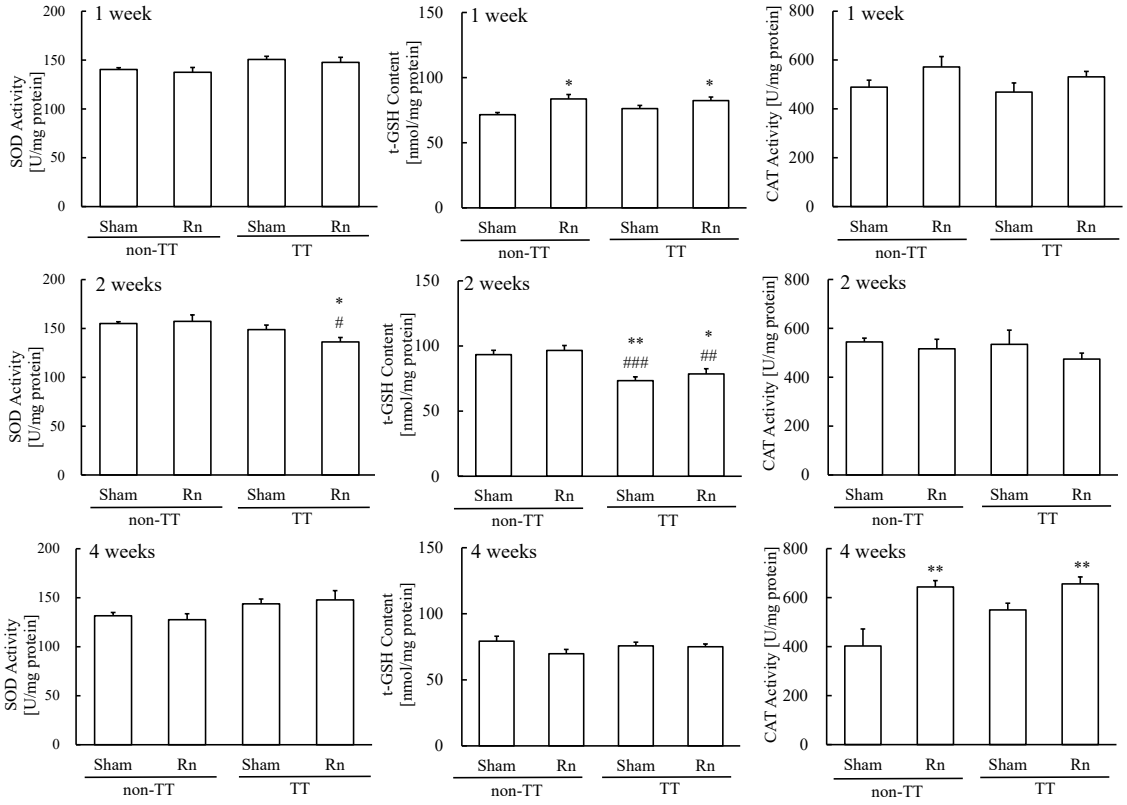

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT
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Fig.3 Liver

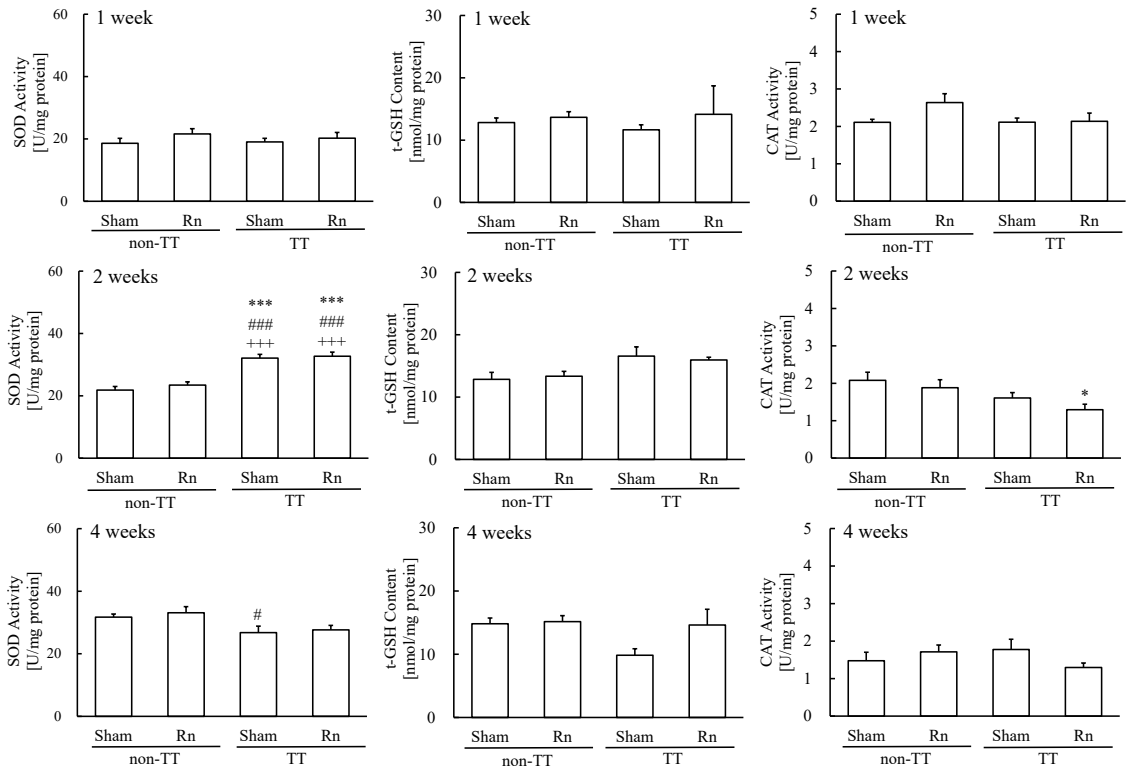


Fig.4 Pancreas

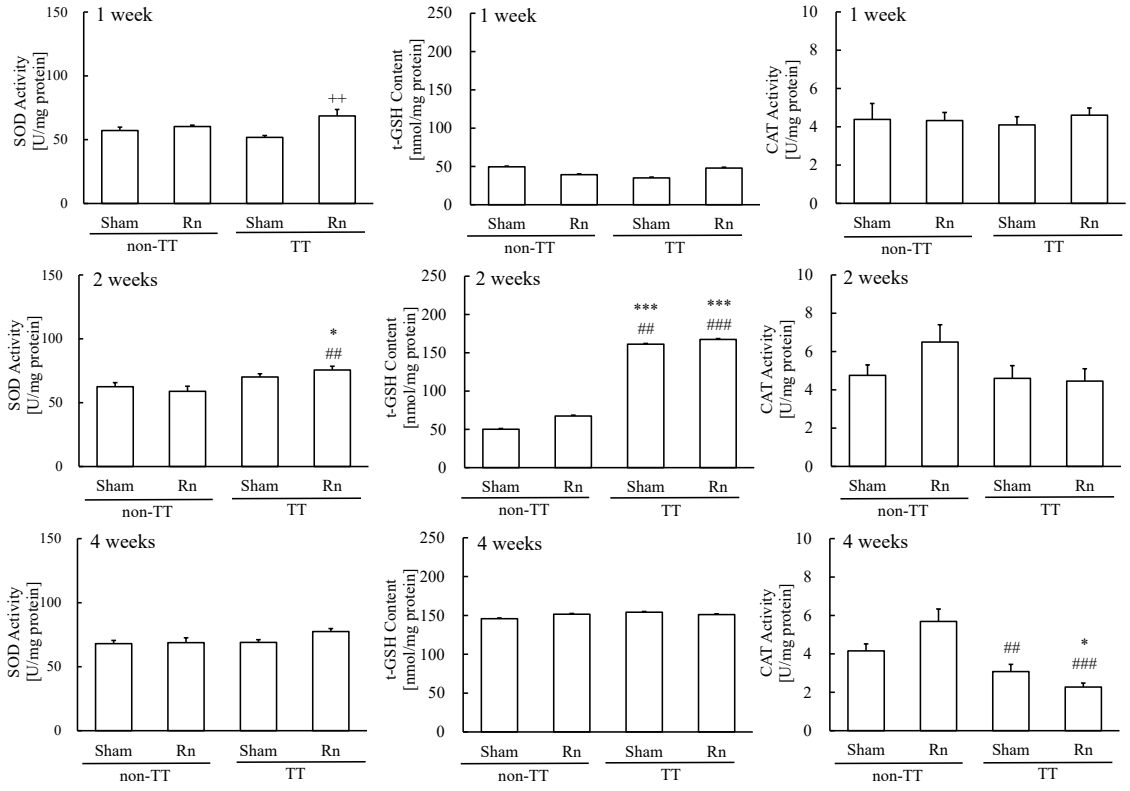

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT
++
*
##
***
###

Fig.5 Colon

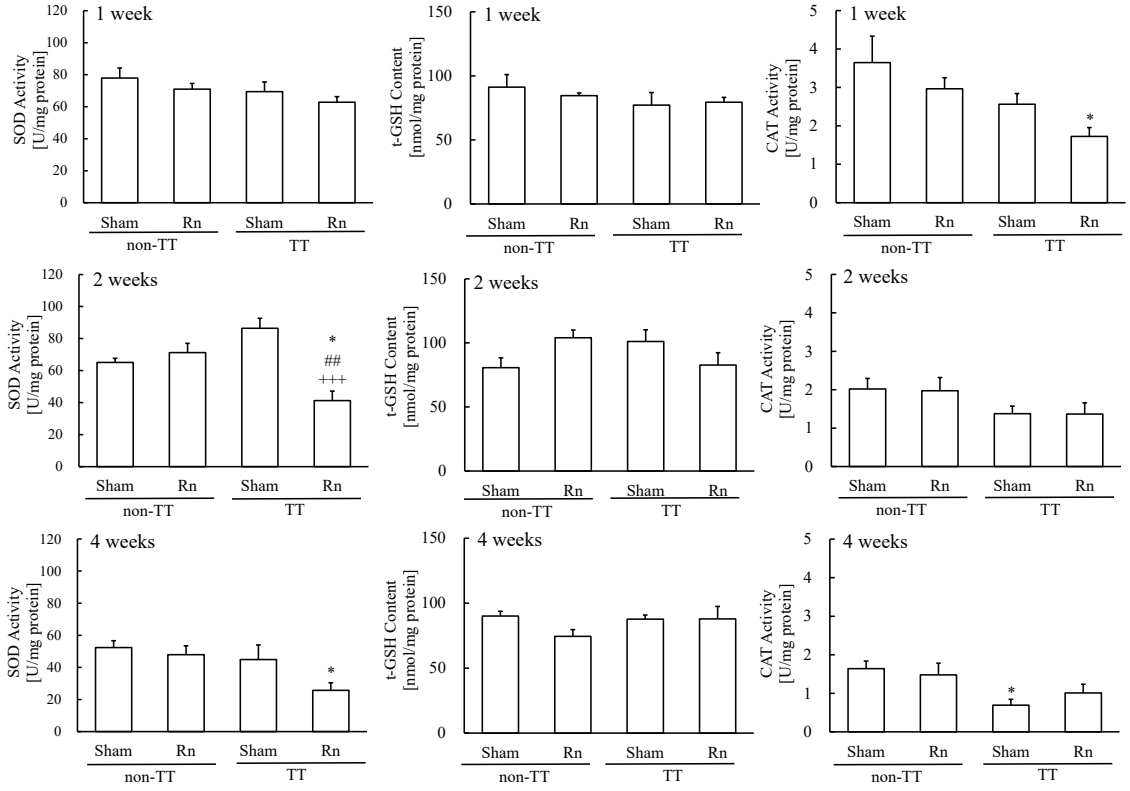

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT
*
##
+++

Fig.6 Brain

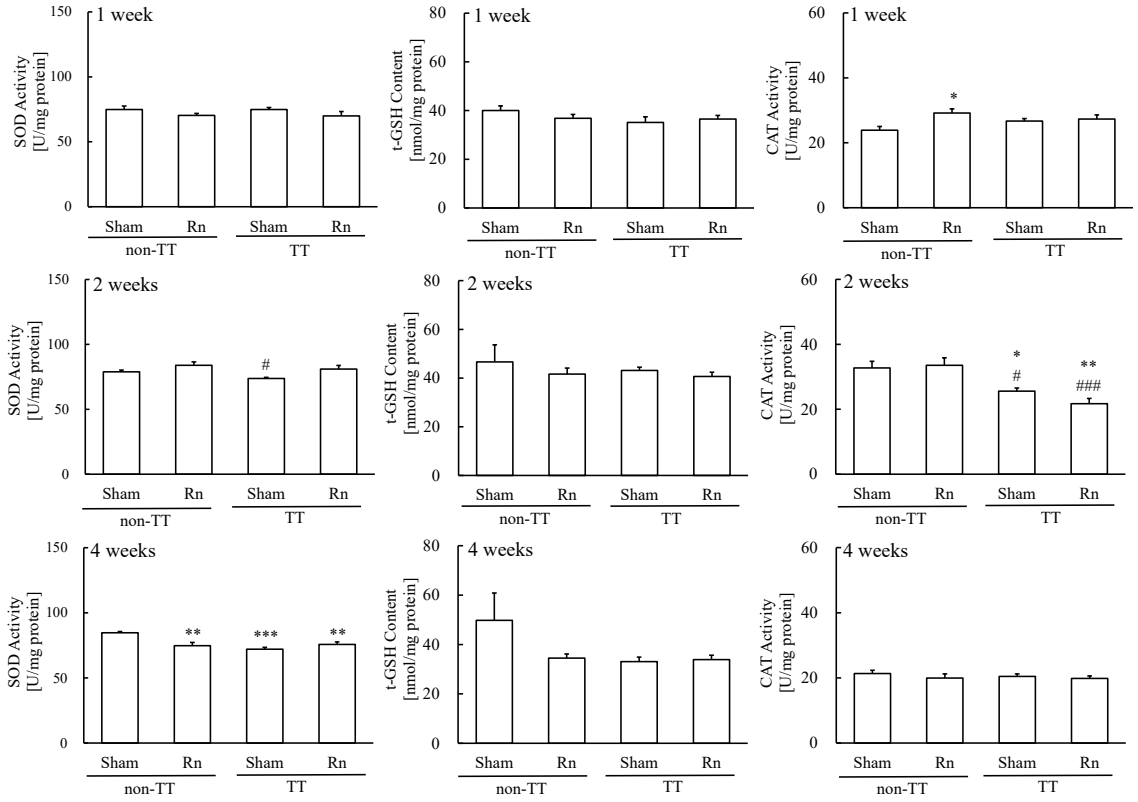

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT

Fig.7 Lung

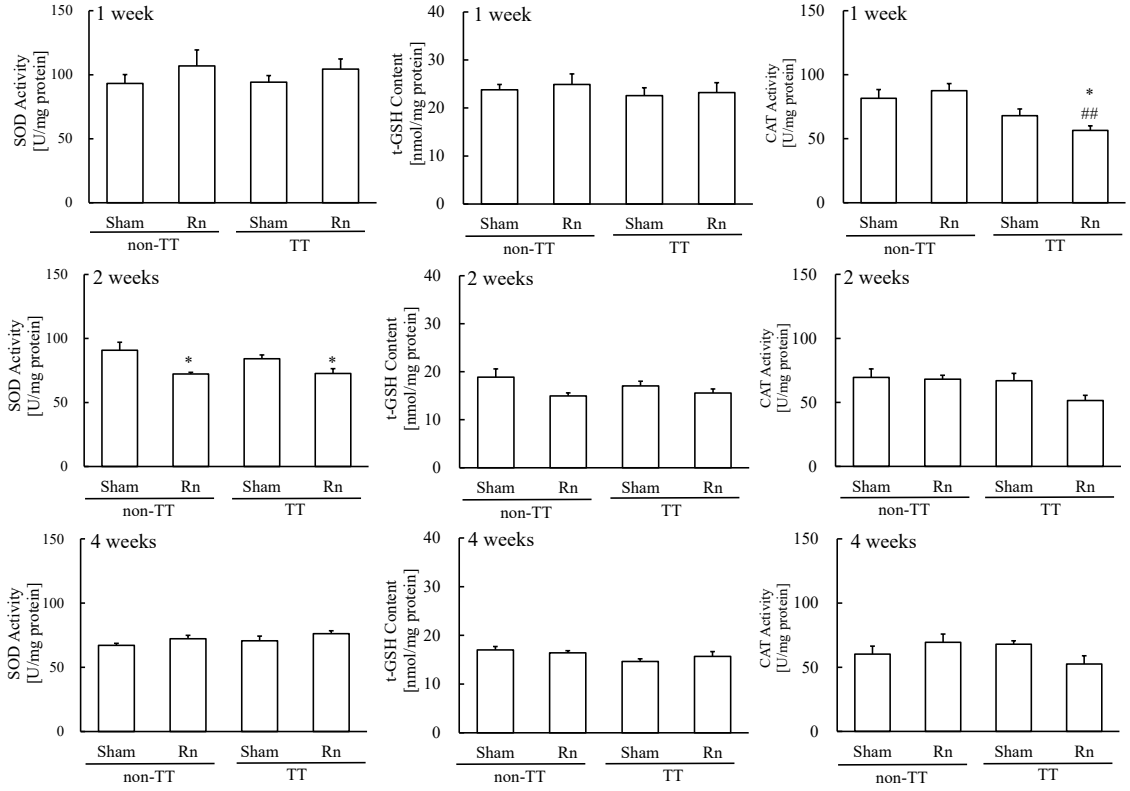

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT
*
##

Fig.8 Kidney

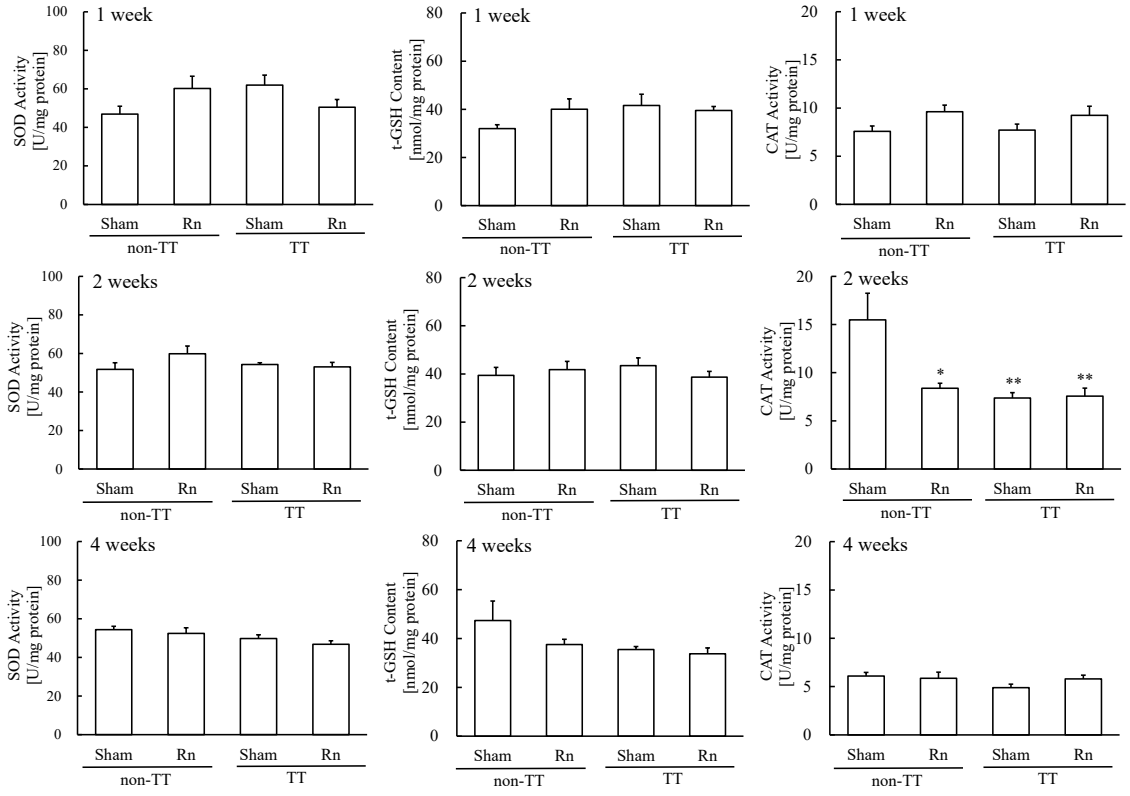


Fig.9 Stomach

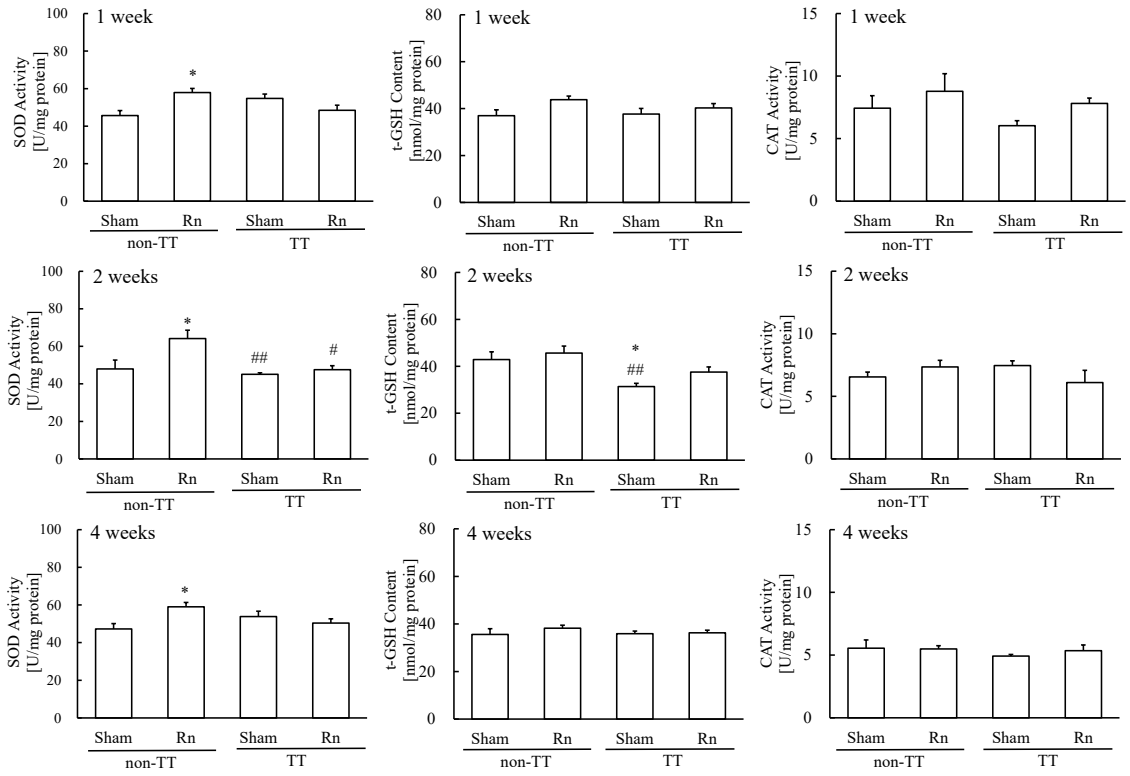

1 week
2 weeks
4 weeks
SOD Activity [U/mg protein]
t-GSH Content [nmol/mg protein]
CAT Activity [U/mg protein]
Sham
Rn
non-TT
TT
*
##
#

Fig.10 Heart

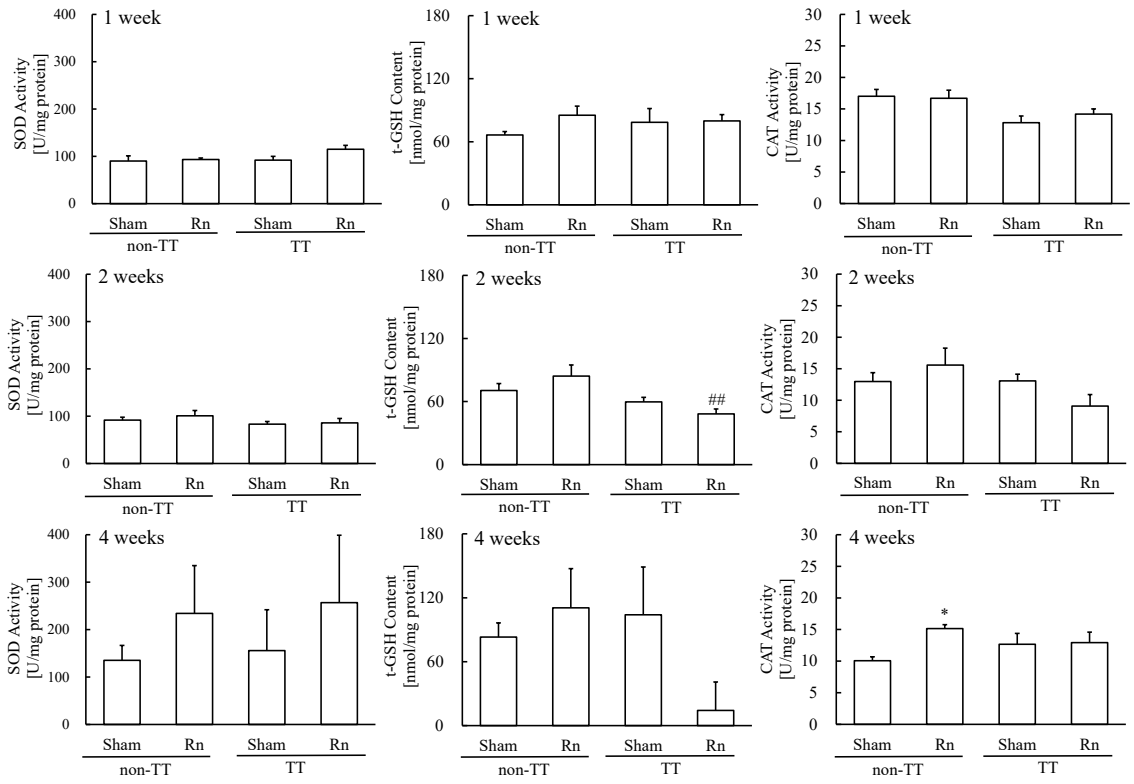


Fig.11 Small intestine